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Behavioural Brain Research 155 (2004) 153–166
BEHAVIOURAL BRAIN RESEARCH
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Research report

The medial septum mediates impairment of prepulse inhibition of acoustic startle induced by a hippocampal seizure or phencyclidine

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Received 16 September 2003; received in revised form 13 April 2004; accepted 13 April 2004

Available online 19 May 2004

Abstract

The involvement of the septohippocampal system on the impaired sensorimotor gating induced by phencyclidine (PCP) or by an electrically induced hippocampal seizure was examined in behaving rats. An impaired sensorimotor gating, measured by prepulse inhibition (PPI) of the acoustic startle response, was observed following a hippocampal afterdischarge (AD) or systemic injection of PCP and was accompanied with an increase in hippocampal gamma waves (30–70 Hz). The medial septum infusion with muscimol (0.25 μg), a $GABA_A$ receptor agonist, 15 min prior to PCP or a hippocampal AD, prevented the impairment of sensorimotor gating and the increase in gamma waves. By itself, muscimol (0.25 μg) injection into the medial septum did not affect PPI, although it significantly suppressed spontaneous gamma waves. In order to identify subpopulations of neurons mediating the sensorimotor gating deficit and the hippocampal gamma wave increase, 0.14–0.21 μg of p75 antibody conjugated to saporin (192 IgG–saporin) was injected into the medial septum to selectively lesion the septohippocampal cholinergic neurons. Neither the PPI deficit nor the gamma wave increase induced by PCP or a hippocampal AD was affected by 192 IgG–saporin lesion of the medial septum. It is concluded that increase in neural activity in the medial septum participates in the impairment of sensorimotor gating and the increase in hippocampal gamma waves induced by PCP or a hippocampal AD. It is suggested that the GABAergic but not the cholinergic septohippocampal neurons mediate the sensorimotor gating deficit.

Keywords: Hippocampus; Medial septum; Brain waves; Seizures; Phencyclidine; Psychoses

1. Introduction

Sensorimotor gating involves the involuntary suppression of motor response by a sensory stimulus [53–55]. A deficit in sensorimotor gating was found in schizophrenic patients [10,54,57]. Sensorimotor gating deficit was also found in laboratory animals after administration of a psychotomimetic drug [4,23,55] and in an animal model of temporal lobe seizures [27].

Prepulse inhibition (PPI) of an acoustic startle response provides a measurement of sensorimotor gating. In the study of prepulse inhibition of acoustic startle, low-intensity noise preceding a loud noise suppresses the startle response elicited by the loud noise. PPI may involve many neural circuits of which the central part is the nucleus accumbens and its descending ventral pallidum output [28,53]. In addition, several studies have demonstrated a critical role of the hippocampus in mediating PPI. Chemical stimulation of different areas of the hippocampus [5,13,56] or excitotoxic lesion of the subiculum in infant [36] or adult rats [56] resulted in PPI deficit. Presumably, the glutamatergic projections of the hippocampus to the nucleus accumbens [19] may directly or indirectly activate dopamine release in the nucleus accumbens [11,30,31] and induce a PPI deficit [53].

A critical brain area that controls the hippocampus is the medial septum. Septohippocampal afferents consist of both

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doi:10.1016/j.bbr.2004.04.010

cholinergic and GABAergic fibers [2,25] that have a profound influence on hippocampal neural activity [8,9,12,34,35]. In previous studies, we have shown that phencyclidine (PCP) [40] or a hippocampal seizure [39] increased hippocampal gamma waves and locomotor activity, and both the gamma wave increase and the behavioral hyperactivity were abolished when the medial septum was infused with muscimol, a $GABA_A$ receptor agonist [39,40]. It is not clear whether the septohippocampal system plays a role in mediating sensorimotor deficits following PCP or a hippocampal seizure. Thus, one of the goals of this study is to investigate the relation between hippocampal EEG, gamma waves in particular, and the PCP-induced PPI deficits. We also studied whether the muscimol infusion into the medial septum suppressed PPI deficits at the same time it altered hippocampal gamma waves. Since a hippocampal afterdischarge (AD) also activated hippocampal gamma waves and behavioral hyperactivity [39], whether PPI deficits were induced by an AD, with or without septal muscimol infusion, was also studied. Selective lesion of the cholinergic neurons in the medial septum was attempted to elucidate the participation of cholinergic septohippocampal afferents in mediating the PPI deficit.

2. Animals and methods

The surgical and recording procedures have been described elsewhere [39]. Briefly, under sodium pentobarbital anesthesia, male Long–Evans rats were implanted with recording electrodes (100 μm Teflon-insulated wires) in stratum radiatum and stratum oriens of the hippocampal CA1 region on both sides (A −3.5, L ±2.7, and ventral (V) from skull surface −2.3 to 3.3; units in mm), according to the stereotaxic atlas of Paxinos and Watson [45]. A guide cannula was implanted dorsal to the medial septum, with the final injections targeted at A 0.7, L 0, V −5.6. In four rats, a guide cannula was placed bilaterally above ventral pallidum such that injections will be targeted at A 1.2, L 1.9, V −5.6 in two rats, and at A −0.3, L 2.3, V −7.8 in the other two rats. Two screws were implanted in the frontal skull and cerebellum to serve as the stimulus anode and recording reference, respectively. Rats were allowed to recover for at least 7 days after surgery. All experimental procedures were conducted according to the guidelines of Canadian Council for Animal Care. Efforts were taken to minimize the pain and suffering of animals.

Hippocampal EEGs were recorded before (5 min of baseline recording) and during prepulse inhibition test. A hippocampal AD was induced by a 1 s, 200 Hz train of stimulus pulses (0.1 ms duration) delivered cathodally to stratum radiatum of the contralateral CA1, at an intensity of three times the commissural evoked potential threshold. Muscimol (0.125, 0.25 and 1 μg in 0.6 μL physiological saline) was infused into the medial septum 15 min before PPI test and EEG recordings. A dose of 0.25 μg muscimol was used for all medial septal injections to examine the effects on impairments of PPI induced by a hippocampal AD or PCP (5 mg/kg i.p.). This dose was chosen according to the preliminary data showing that infusion of 0.01 μg ($n = 1$), 0.1 μg ($n = 1$) or 0.125 μg ($n = 2$) of muscimol into the medial septum did not show an obvious antagonistic effect on PPI deficit induced by PCP (5 mg/kg) or a hippocampal AD. In addition, as compared to a 0.25 μg dose, 0.5 μg of muscimol ($n = 2$) showed a similar blocking effect on the impairment of PPI, but a more robust suppression of locomotion induced by PCP (5 mg/kg i.p.) or a hippocampal AD. Bland et al. [9] showed that the minimum dose of muscimol injected into the medial septum that suppressed spontaneous or hypothalamic stimulation-induced hippocampal theta activity was 5 nmol (equal to 0.571 μg); the theta waves were totally abolished at a dose of 10 nmol (1.14 μg). Four rats received 0.1 μg/0.5 μL muscimol or saline in the ventral pallidum prior to PCP ($n = 2$) or a hippocampal AD ($n = 2$). Our previous study of hippocampal population spike recording and dye diffusion indicated that 1.0 μg of muscimol in 0.6 μL affected a volume of ∼1 mm radius in <30 min [41].

The EEG signals were filtered between 0.3 and 100 Hz and recorded on a polygraph (Grass 7D) and sampled at 200 Hz by a microcomputer. Baseline EEG was recorded for 5 min in all experiments in the startle chamber. Thereafter, the animal was removed from the chamber to receive medial septal injection of saline or muscimol and waited for 15 min. For PCP experiment, the rat would subsequently receive PCP injection and wait for another 15 min. Then, the animal was put back into the startle chamber and reconnected to the recording/stimulating cable. For hippocampal AD experiments, 15 min after the rat received septal muscimol/saline injection, the rat was returned to the startle chamber where the AD was delivered, and PPI data were collected starting 2 min after the AD. Twelve minutes of hippocampal EEG was recorded in the startle chamber during the whole period of PPI test. At least 30 s of EEG was manually selected from each minute of EEG recording and subjected to power spectral analysis, using segments of 5.12 s (1024 points sampled at 200 Hz [32]). Thus, the average power spectrum was derived from at least 2.5 min of baseline EEG, and 6 min of EEG during PPI. The power spectra were plotted in logarithmic units, with calibration of 6.15 log units = 1.0 mV peak-to-peak sine wave. Gamma power was measured by the mean integrated power in the gamma frequency band of 30–70 Hz (sum of power within the frequency band divided by the bandwidth). The change in hippocampal gamma waves was calculated by difference of the mean integrated gamma power during PPI test and that during baseline recording.

An 8.2 cm diameter Plexiglas cylinder served as the startle chamber (SR-LAB, San Diego Instruments, San Diego, CA). A piezoelectric accelerometer was used to detect startle amplitude, and bursts of acoustic noise were given by a loudspeaker mounted 24 cm above the rat. An IBM-compatible microcomputer with SR-Lab software and

interface was used to present acoustic stimuli and to record data. During PPI testing, a rat was put in the startle chamber for a 5 min acclimation period with a 68 dB background noise. After an acclimation period, the rat was given four types of stimuli: (i) startle pulse (120 dB 40 ms broad band burst); and (ii) each of prepulse (73, 75, or 80 dB 20 ms broad band) presented 100 ms prior to startle pulse. The session was designed with five trial types: startle pulse alone, each of three prepulse trials followed by a startle pulse or a period of no acoustic stimulation. For each test session, 50 trials (10 startle pulse, 10 no stimulation, and 10 of each prepulse trial types) were given in randomized order. The intertrial interval was 15 s. Each test session was repeated twice. PPI was measured as the difference of the response to the startle pulse alone and that to prepulse-startle, or PPI (in %) $= 100 \times [1 - (\text{mean startle response amplitude for prepulse-startle trial/mean amplitude of response to startle alone})]$. In this study, mean values of the prepulse intensity of 73, 75, 80 dB (integrated prepulse intensity) and each of the three types of intensity was used for calculation of the percentage of the PPI. In order to eliminate the possible influence of startle amplitude on prepulse inhibition, rats with similar startle amplitude were selected for both control and experimental groups. In some groups of rats, the relation between percent of prepulse inhibition (%PPI as Y) and startle amplitude (as X) was plotted and subjected to linear regression analysis. The best curve $Y = A + BX$ was determined, and the statistical significance of the deviation of B from zero, was evaluated by t-statistics.

Horizontal movements (locomotion) of a rat were measured by the number of interruptions of infrared beams in a Plexiglas chamber (69 cm × 69 cm × 49 cm). Four independent infrared sources, at 23 cm intervals, were located on a horizontal plane 5 cm above the floor, with photodiode detectors on the other side. Interrupts of the beams were counted and transferred to a microcomputer via an interface (Columbus Instruments). Before the start of an experiment, a rat was habituated for at least 1 h in the chamber. For experiments on hippocampal AD, spontaneous locomotor activity was recorded for 10 min baseline (before any drug), and 10 min (2 min counts) following a hippocampal AD. Either muscimol (0.25 μg/0.6 μL) or saline (0.6 μL) was injected into the medial septum, 15 min before the AD. For the PCP experiments, either muscimol or saline (same dose as earlier) was infused into the medial septum 15 min before PCP (5 mg/kg i.p.). Spontaneous locomotor activity was recorded during baseline and for 5–120 min (at 10 min intervals) after PCP.

P75 receptor antibody conjugated to saporin (192 IgG–saporin stock) solution (Chemicon, Temecula, CA) was diluted to 0.21 μg/0.6 μL with sterile saline. Rats given control injections using saline will be referred to as the sham lesion group. This solution was then infused into the medial septum at a constant rate of 1 μL/2min by a Grass infusion pump, via 30-gauge Hamilton syringe. Two types of injections were done: midline injections (L 0; $n = 3$ for 192 IgG–saporin and $n = 3$ for saline) and paramidline bilateral injections (L 0.5; $n = 8$ for 192 IgG–saporin at 0.14 μg/0.4 μL per side and $n = 4$ for saline). The injection needle remained in place for 10 min before retraction to allow diffusion of the solution. Hippocampal EEG was monitored in all saporin and sham lesion rats 2 days after lesion and experiments were started 7–10 days after lesion.

At the end of experiments, saporin and sham lesion rats were given a surgical anesthetic dose of pentobarbital and

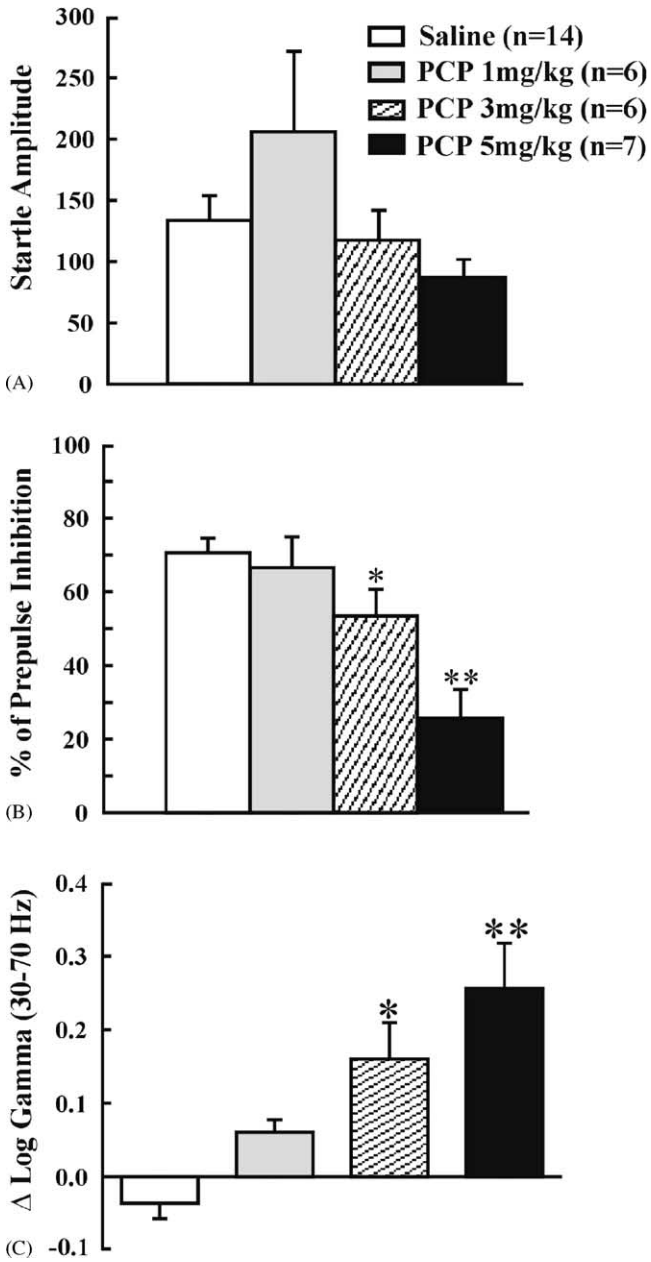

Fig. 1. Effects of different doses of phencyclidine (PCP) on acoustic startle response (A), prepulse inhibition calculated by integrated prepulse intensity (B), and change in logarithmic gamma power, integrated over 30–70 Hz (C). $^{*}P < 0.05$; $^{**}P < 0.01$, difference from saline control, paired t-test.

perfused through the heart with 100 mL saline followed by 400 mL of 4% paraformaldehyde solution (Sigma) in 0.1 M phosphate buffer (PB; pH 7.4). The rat brain was removed and post-fixed with 18% sucrose in phosphate-buffered saline for 24 h at 4 °C. For immunocytochemistry of choline acetyltransferase (ChAT) and parvalbumin (Parv), sections were incubated first in 10% normal goat serum in 0.1 M PB containing 0.01% Triton X-100 (Sigma) for 1 h at room temperature to block non-specific labeling. The sections were rinsed briefly in PB and incubated at 4°C for 48 h in primary antibody solution containing mouse monoclonal ChAT (1:200; Biogenesis) or mouse monoclonal parvalbumin (1:2000, Sigma) and 1% normal goat serum. Sections were washed in three changes of PB and followed by biotin-conjugated goat anti-mouse secondary antiserum (1:200; BioCan) for 1 h in room temperature. The sections were then washed several times in PB solution. ABC complex was prepared by adding equal volumes of solutions A and B mixed with PB (1:1:100) 20 min before use (standard ABC reagent; Vector Laboratories). The sections were incubated in the ABC solution for 1 h at room temperature. Following three more washes in PB, the sections were incubated in a fumehood in a solution containing 0.05% diaminobenzidine tetrahydrochloride (DAB; Sigma) and 0.003% hydrogen peroxide in PB at room temperature until they reached the desired color intensity (1–3 min). The sections were then washed several times in PB, mounted on chrome-alum gelatin-coated slides. They were dehydrated in a series of 70, 95 and 100% ethyl alcohol, cleared in xylene (5 min, 2×) and cover-slipped with Entellan (BDH) mounting medium.

The sites of cannula injection and the electrodes placements were verified histologically in 40 μm frozen sections of the brain stained with thionin. The number of ChAT- or Parv-positive cells was quantified in three representative coronal sections (40 μm) at anterior (A ∼0.9), middle (A ∼0.4) and posterior (P ∼0.1) levels of the medial septum-diagonal band of Broca region. Selected sections were captured with a digital camera using ×10 magnification

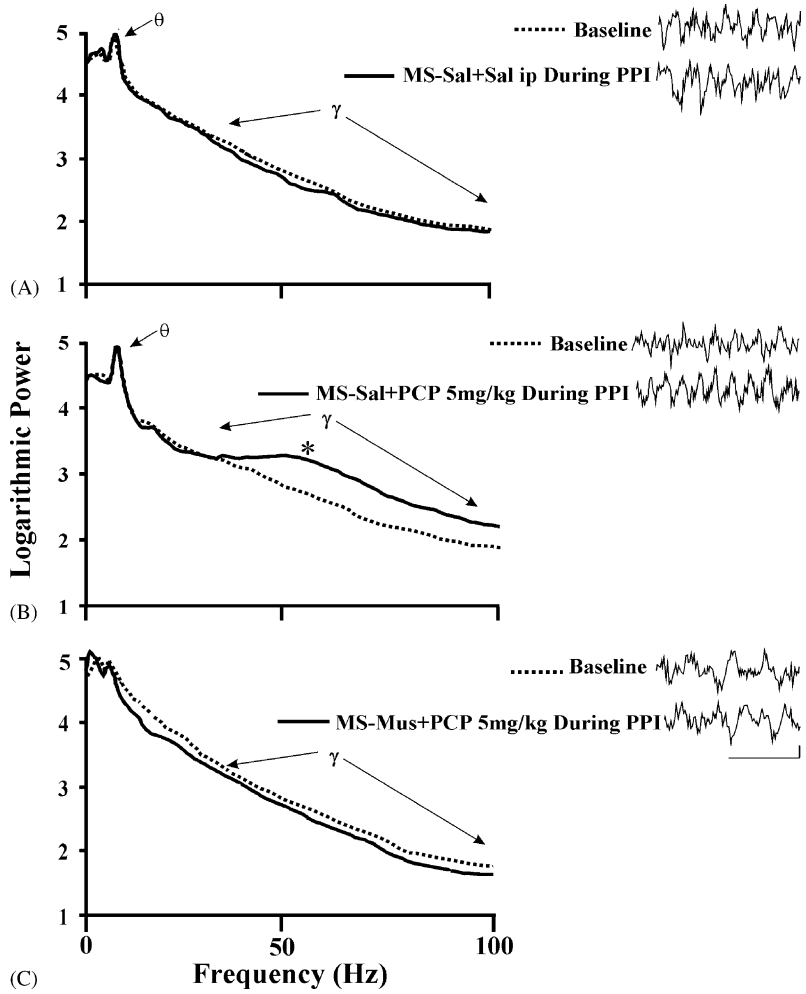

Fig. 2. Representative power spectra of hippocampal EEG recorded at stratum radiatum before (baseline) and during prepulse inhibition (PPI) for different conditions: (A) control with no drug injection; (B) medial septal saline injection (MS-Sal) followed by i.p. PCP (5 mg/kg); (C) medial septal muscimol 0.25 μg injection (MS-Mus) followed by i.p. PCP (5 mg/kg). The asterisk indicates an increase in hippocampal gamma waves. The insets are samples of the corresponding raw EEG. Calibration: 125 μV (vertical), 0.5 s (horizontal).

in a Nikon microscope, and cells were counted from the digital images.

Statistical analyses were performed using paired *t*-test (two-tailed), one-way or two-way repeated measure analysis of variance (ANOVA), followed by Newman–Keuls' post hoc test. *P*-values of <0.05 were considered to be statistically significant.

3. Results

3.1. Effects of PCP on PPI and hippocampal gamma waves

The dose effects of PCP on PPI and startle amplitude are shown in Fig. 1. PCP at the doses used in this study did not significantly affect startle amplitude compared to saline control (Fig. 1A). PCP at dose of 1 mg/kg did not significantly change PPI, but higher doses of 3 and 5 mg/kg i.p. induced a significant impairment (decrease) of PPI, calculated by the integrated prepulse intensity ($t = 3.31$, $P < 0.05$ and $t = 4.19$, $P < 0.01$, respectively; Fig. 1B) or at each prepulse intensity of 73 dB ($t = 2.84$, $P < 0.05$ and $t = 3.79$, $P < 0.01$, respectively), 75 dB ($t = 3.38$, $P < 0.05$ and $t = 3.95$, $P < 0.01$, respectively) and 80 dB ($t = 2.77$; $P < 0.05$ and $t = 5.06$; $P < 0.01$, respectively).

Hippocampal EEG was recorded in the startle chamber before (baseline) and during the PPI procedure (see Section 2). For control rats that received saline injections into the medial septum, the hippocampal EEG recorded during PPI did not differ from the baseline recordings (Figs. 1C and 2A). Hippocampal theta rhythm accompanied head and body movements of a rat [8,12,32,35] during the baseline and partial confinement in the startle chamber, and there was no consistent change of theta power following PCP treatment as compared to the baseline (Fig. 2B). However, hippocampal gamma waves were significantly increased following administration of PCP (Figs. 1C and 2B). The increase was dose dependent and significant increase of gamma waves was found after PCP at doses of 3 mg/kg i.p. ($t = 3.07$, $P < 0.05$) and 5 mg/kg i.p. ($t = 6.32$, $P < 0.01$; Fig. 1C).

3.2. Medial septal muscimol infusion abolished PCP-induced change in PPI and hippocampal gamma waves

The involvement of the medial septum on PPI was studied by injection of various doses of muscimol into the medial septum. The injection sites were verified to be in the medial septum (Fig. 3). Muscimol injection by itself, at a dose of 0.125, 0.25 or 1 μg, did not significantly affect startle amplitude ($F(3, 23) = 0.57$, $P > 0.05$, one-way ANOVA; Fig. 4A) or PPI calculated by the integrated prepulse intensity ($F(3, 23) = 1.55$, $P > 0.05$, one-way ANOVA; Fig. 4B) or at each individual prepulse intensity (not shown). By contrast, the power of hippocampal gamma waves was decreased by intraseptal injection of muscimol in a dose dependent manner ($F(3, 23) = 9.11$, $P < 0.001$, one-way ANOVA; Fig. 4C). Muscimol at a dose of 1 μg injected into the medial septum decreased hippocampal theta peak power in the startle chamber by 0.39 ± 0.11 log units, significantly more than 0.09 ± 0.03 log units after saline injection into the medial septum ($P < 0.05$, paired *t*-test). Muscimol injected into the medial septum at a dose of 0.125 or 0.25 μg did not significantly change theta power in the startle chamber as compared to saline injection ($P > 0.5$, paired *t*-test).

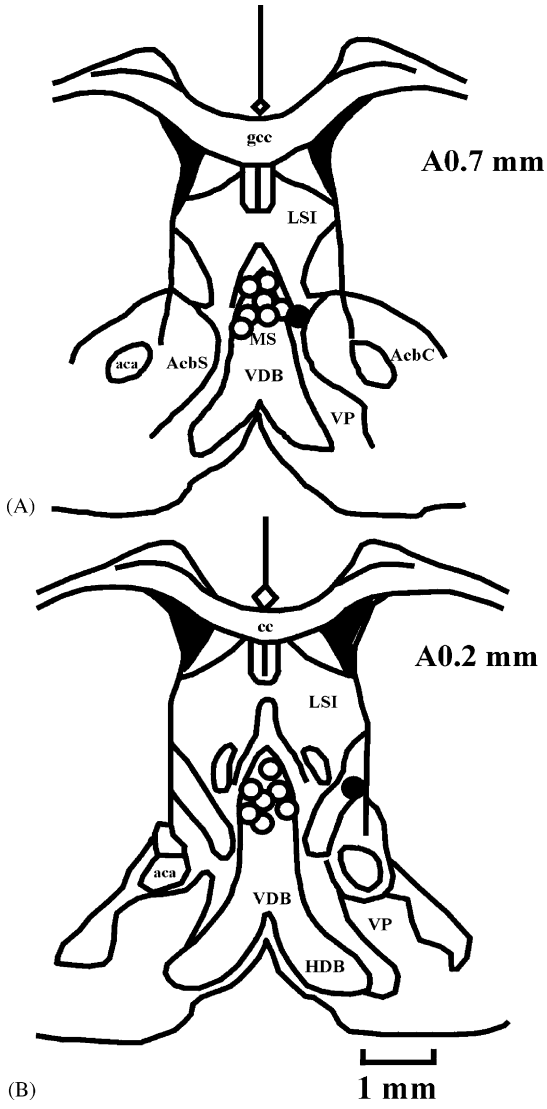

Fig. 3. Schematic coronal brain section at 0.2 and 0.7 mm anterior to bregma showing injection sites modified from Paxinos and Watson [45]. Open circles illustrate inner cannulae injection sites as confirmed by glial tracks. Fourteen injected sites from 14 rats were indicated. Solid circles indicate sites outside of the medial septum, which were excluded from analysis. *Abbreviations*: AcbC, nucleus accumbens, core; AcbS, nucleus accumbens, shell; aca, anterior commissure, anterior; cc, corpus callosum; gcc, genu corpus callosum; HDB, horizontal limb diagonal band of medial septum; LSD, dorsal lateral septum; LSI, intermediate lateral septum; LSV, ventral lateral septum; MS, medial septum; SH, septohippocampal nucleus; VP, ventral pallidum.

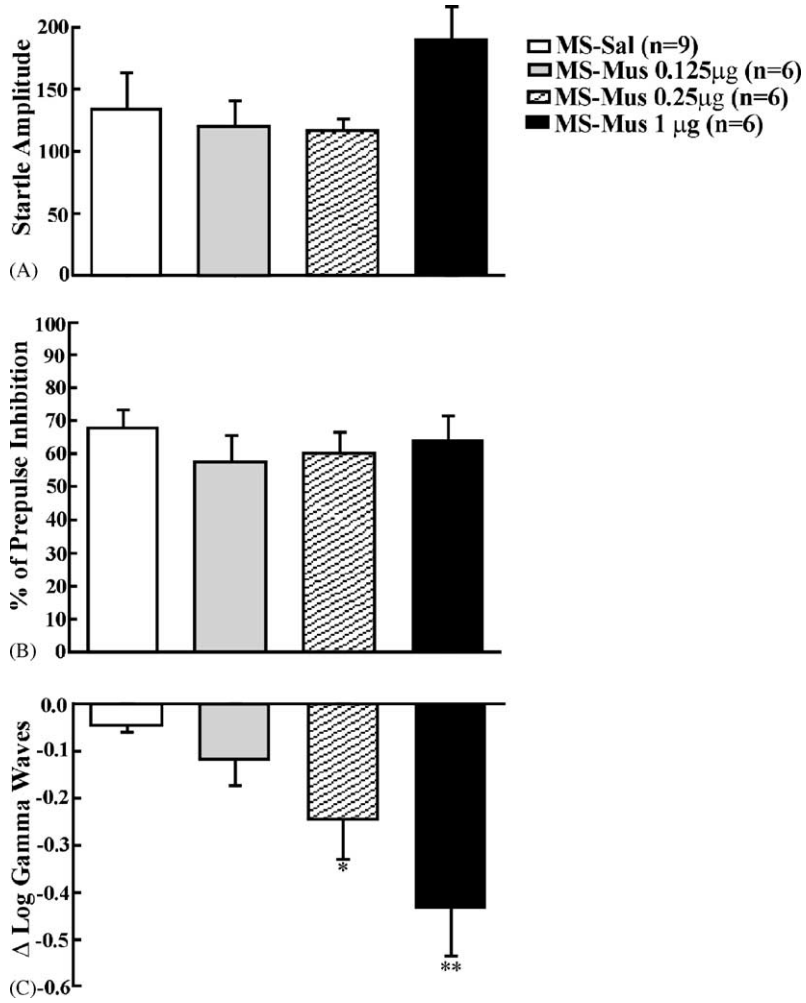

Fig. 4. Effect of different doses of muscimol injected into the medial septum alone on acoustic startle responses (A), prepulse inhibition calculated by integrated prepulse intensity (B), and the change in logarithmic hippocampal gamma power (C). $^{*}P < 0.05$; $^{**}P < 0.01$, difference from control saline injections (Newman–Keuls' post hoc test after one-way ANOVA).

While there was no difference in startle amplitude among the subgroup of different treatments ($F(2, 25) = 0.019$, $P = 0.98$; Fig. 5A), septal muscimol injection abolished the effects of PCP (5 mg/kg i.p.) on PPI calculated by integrated prepulse intensity. In rats given pre-injection of saline into the medial septum, PCP induced an impairment of PPI (septal saline + saline i.p. versus septal saline + PCP; $t = 4.31$, $P < 0.01$); the PPI impairment was similar to rats without saline septal injections, as reported earlier. However, pre-injection of muscimol (0.25 μg/0.6 μL) into the medial septum significantly decreased the PPI impairment induced by PCP (septal saline + PCP versus septal muscimol + PCP; $t = 2.99$, $P < 0.05$; Fig. 5B). PCP induced a significantly increase in hippocampal gamma waves in rats pretreated with saline injection into the medial septum ($t = 4.66$, $P < 0.01$). However, if muscimol was injected into the medial septum, no enhancement of hippocampal gamma waves was found after PCP (Figs. 2C and 5C). In summary, 0.25 μg of muscimol injected into the medial septum abolished the PPI impairment and the gamma waves increase induced by PCP.

3.3. Hippocampal afterdischarge as another model to induce PPI impairment

A hippocampal AD induced an increase in hippocampal gamma waves and behavioral hyperactivity similar to PCP (3–5 mg/kg i.p.) injection. Thus, the effects of a hippocampal AD on PPI and hippocampal gamma waves were also studied.

The startle amplitudes were similar among three groups of rats—one group with given no AD but only saline injection (i.p. or septal), and the other two groups given a hippocampal AD, either preceded with saline or muscimol injection in the medial septum ($F(2, 26) = 0.85$, $P = 0.44$; Fig. 6A). Rats given a hippocampal AD showed a significantly decreased PPI as compared to control rats not given an AD, as calculated by the integrated prepulse intensity ($F(2, 26) = 19.65$, $P < 0.0001$, Fig. 6B). The plot of %PPI with startle amplitude revealed that %PPI was not dependent on startle amplitude, and the slope of the linear regression line of %PPI versus startle amplitude (see Section 2) was

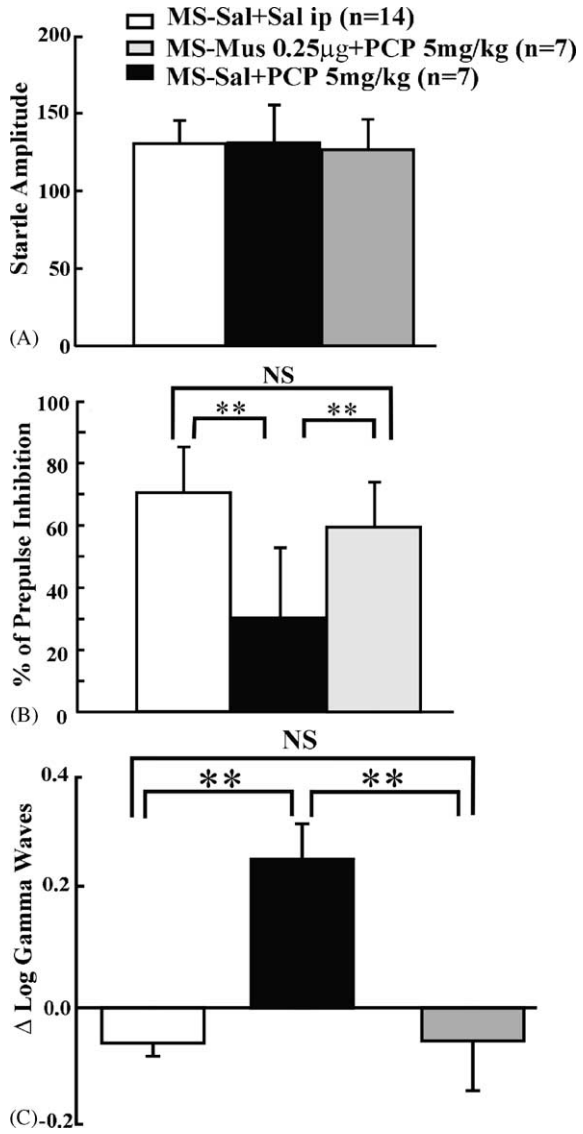

Fig. 5. Effect of medial septal muscimol infusion on acoustic startle response (A) and prepulse inhibition calculated by integrated prepulse intensity (B), and change in logarithmic integrated gamma power (C) following PCP (5 mg/kg i.p.) injections. $^{**}P < 0.01$, paired comparison (*t*-test). NS: not significant.

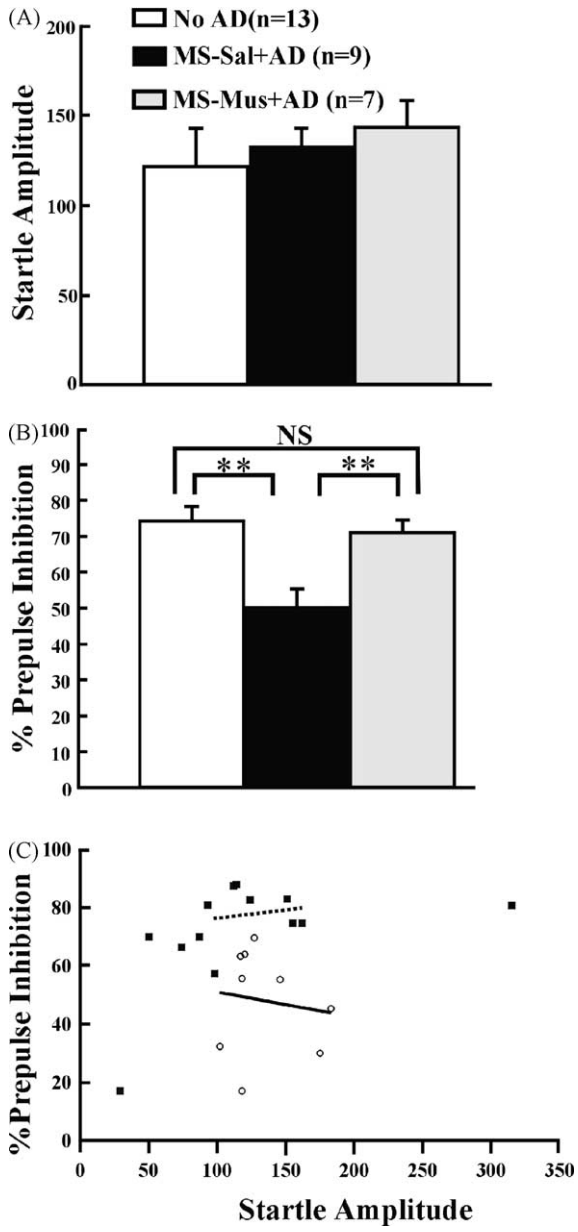

Fig. 6. Effects of a hippocampal AD on acoustic startle response (A) and prepulse inhibition calculated by integrated prepulse intensity (B). $^{*}P < 0.05$; $^{**}P < 0.01$, paired comparison (Newman–Keuls' post hoc test after one-way ANOVA). NS: not significant. (C) Scatter plot of the integrated PPI vs. startle amplitude for individual control (solid squares) and AD (open circles) experiments. Linear regression lines are shown for the %PPI vs. startle amplitude data, within the range of startle amplitudes (95–180 units) common to the control (dotted line) and AD (solid line) experiments. The regression line for each group is $Y = A + BX$, where Y is the %PPI, X the startle amplitude, A the y-intercept, and B the slope. The slope B was not statistically different from zero for any group.

not significantly different from zero ($P > 0.05$) for any group of rats. For the two groups (septal saline + AD and septal muscimol + AD) shown in Fig. 6C, the %PPI values were significant different between the two groups within a fixed range of startle amplitudes ($P < 0.003$, Wilcoxon test or *t*-test, for startle amplitude range of 95–180 units).

Hippocampal gamma waves were significantly increased after an AD, as compared to baseline ($F(2, 24) = 15.24$, $P < 0.0001$; Fig. 7A and B). Thus, septal infusion with muscimol abolished the changes in hippocampal gamma and PPI after an AD. PPI impairment was not found if a hippocampal AD was induced after pre-injection of muscimol into the medial septum (0.25 μg/0.6 μL) as compared to pre-injection of saline into the medial septum (Fig. 6B). Muscimol injection into the medial septum blocked the post-ictal increase in gamma waves (Fig. 7A and C) but it did not affect the duration of a hippocampal AD (AD durations in saline- and muscimol-injected rats were 27 ± 2 and 28 ± 3 s, respectively; $t = 0.39$, $P = 0.7$).

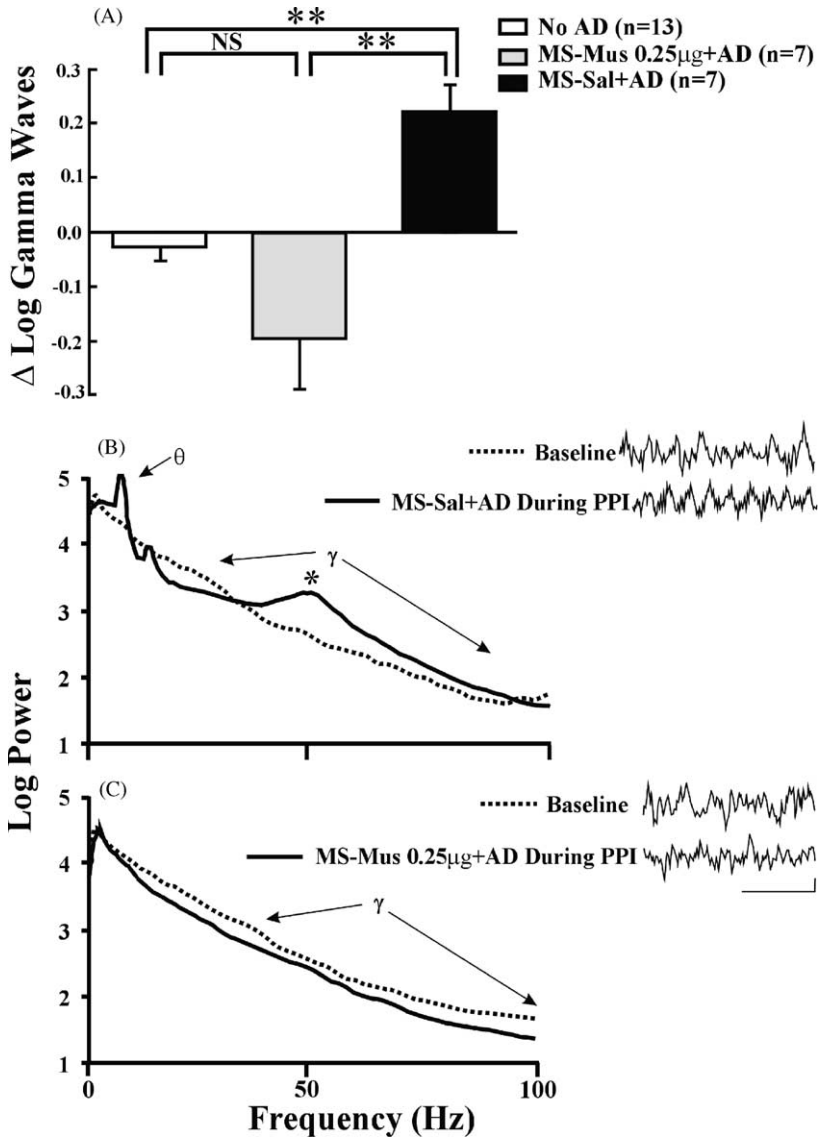

Fig. 7. Changes in gamma waves after an AD, with or without septal muscimol infusion. (A) Changes in integrated gamma power after a hippocampal AD with or without medial septal muscimol infusion of a dose of 0.25 μg. $^{**}P < 0.01$, difference between groups (Newman–Keuls' post hoc test after one-way ANOVA). NS: not significant. (B and C) Representative power spectra of hippocampal EEG recorded at stratum radiatum before (baseline) and during prepulse inhibition (PPI) in different conditions: (B) after medial septal saline (MS-Sal) followed by a hippocampal AD; (C) after medial septal muscimol (MS-Mus) followed by a hippocampal AD. The asterisk indicates the increase in hippocampal gamma waves after a hippocampal AD. The insets are corresponding raw EEG traces. Calibration: 125 μV (vertical), 0.5 s (horizontal).

3.4. Low dose muscimol in ventral pallidum did not clearly affect PPI impairment after PCP or hippocampal AD

There was no clear change in the PPI deficits induced by PCP (two rats), or by an AD (two rats), after direct injection of muscimol (0.1 μg/0.5 μL) into the ventral pallidum (VP). The PPI values (average in two rats) were: after saline i.p. + saline in VP or saline i.p. alone, 60%; PCP + saline in VP, 18%; PCP + muscimol in VP, 21%). The PPI values after a hippocampal AD (average of 2 rats) were: with saline in VP, 14%; with muscimol in VP, 30%). Thus, 0.1 μg of muscimol injected in the VP did not appear to affect PPI greatly.

3.5. The medial septal muscimol infusion attenuated behavioral hyperactivity induced by PCP or hippocampal AD

Locomotor activity was increased after i.p. injection of PCP (5 mg/kg i.p.) and lasted for at least 2 h, and this increase was significantly reduced by intraseptal injection of muscimol (0.25 μg/0.6 μL) ($t = 2.95$, $P < 0.05$, paired *t*-test; data not shown). Similarly, locomotor activity increased after a hippocampal AD, and this increase in locomotor activity was partially but significantly ($t = 4.78$, $P < 0.01$, paired *t*-test) suppressed by intraseptal injection of muscimol (data not shown).

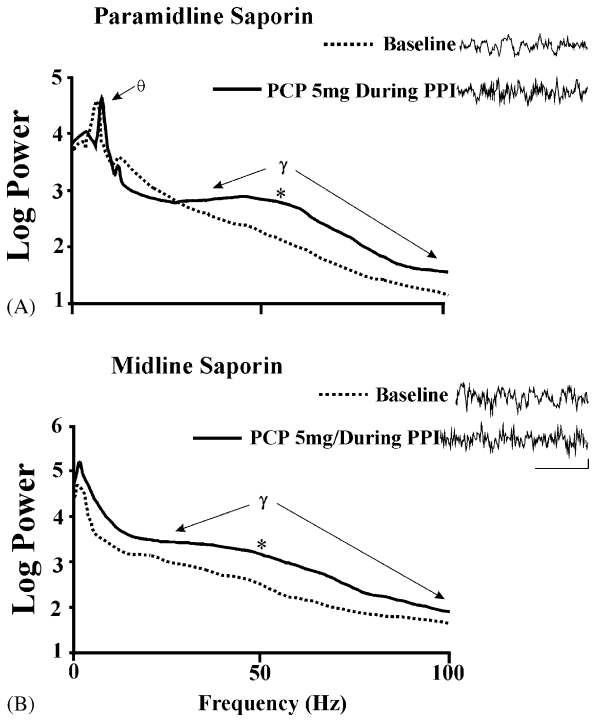

Fig. 8. Representative power spectra of hippocampal EEG recorded at stratum radiatum 21 days after paramidline (A) or midline (B) lesion of the medial septum with 192 IgG–saporin during the baseline or after PCP (5 mg/kg) while PPI tests were conducted. The asterisk indicates an increase in hippocampal gamma waves. Calibration: 125 μV (vertical), 0.5 s (horizontal).

3.6. Septal cholinergic lesion did not affect sensorimotor gating and hippocampal gamma waves

The spontaneous theta rhythm during baseline walking was totally abolished 1 week after midline injection of 192 IgG–saporin (three rats; Fig. 8B). After paramidline 192 IgG–saporin injections (eight rats), theta rhythm was reduced but not abolished (Fig. 8A), as compared to sham lesion rats with saline injected into MS. The spontaneous gamma waves during baseline were not different between sham lesion and 192 IgG–saporin lesion rats (SAP-lesion), regardless of midline or paramidline injections.

After 5 mg/kg i.p. PCP, SAP-lesion rats showed a robust increase in hippocampal gamma waves (Figs. 8 and 9A) compared to that of SAP-lesion followed by saline i.p. injection ($t = 4.61$, $P < 0.01$). There was no difference in gamma waves between SAP-lesion and control non-lesion rats (Fig. 9A). Similarly, SAP-lesion rats showed a significant ($t = 4.89$, $P < 0.01$) increase in hippocampal gamma after a hippocampal AD compared to that of SAP-lesion with no AD rats (Fig. 9B). SAP-lesion rats were not different from sham lesion rats in the startle amplitude (Fig. 10A) or PPI (Fig. 10B), and they showed PPI impairment after PCP (5 mg/kg i.p.) injections compared to saline i.p. injections ($t = 2.94$, $P < 0.05$; Fig. 10B). Similar to non-lesion or sham lesion animals, PPI impairment was found after a hippocampal AD in SAP-lesion rats, as compared to no AD ($t = 3.47$, $P < 0.05$; Fig. 10D), and startle amplitude was not affected in SAP-lesion rats compared to sham lesion rats (Fig. 10C).

Table 1
Choline acetyltransferase (ChAT)- and parvalbumin (Parv)-immunoreactive cells in the medial septum, following 192 IgG–saporin (SAP) or control injections

Group	ChAT-positive cells	Parv-positive cells
Midline SAP	37 ± 2 (2)	119 ± 6 (2)
Paramidline SAP	11 ± 6 (7)	561 ± 120 (7)
Paramidline control	784 ± 201 (6)	568 ± 90 (6)
P	<0.05	NS

Some paramidline control rats were not assessed in the PPI. The number of ChAT- or Parv-positive cells was assessed in a standard field in the medial septum (~1 mm × 1 mm centered at A ~0.4, V −6). Number of rats in brackets after mean ± S.E.M. *P* indicates statistical results. NS: not significant.

SAP-lesion rats showed an obvious loss of ChAT-immunoreactive neurons in the medial septum (Fig. 11). More than 90% of the ChAT-containing neurons in the medial septum disappeared after midline or paramidline lesions (Table 1 and Fig. 11). The number of parvalbumin-containing neurons was not significantly different between saline-injected and paramidline SAP-lesion rats (Table 1 and Fig. 11).

4. Discussion

The present study demonstrated that sensorimotor gating, as indicated by PPI, was impaired after a hippocampal seizure or a single dose of PCP, and that the PPI impairment was accompanied by abnormal, high-amplitude hippocampal gamma waves. The medial septal muscimol infusion of a 0.25 μg dose, but not 192 IgG–saporin lesion of the cholinergic septohippocampal neurons, suppressed the hippocampal gamma waves and the behavioral abnormalities (hyperlocomotion, PPI deficit) induced by PCP or a hippocampal AD.

4.1. Gamma brain waves and cognitive processing

Gamma waves have been suggested to be important for normal information processing in the brain. For example, by synchronizing neural signals across large areas of the visual cortex, gamma waves may perform binding of the different features of an object into a percept [50]. Here, we reported that the high-amplitude hippocampal gamma waves induced by PCP or by an electrical seizure were correlated with abnormal behaviors measured as hyperlocomotion and PPI impairment.

Schizophrenic patients were reported to show increased fast EEG waves [1,20], which decreased after effective treatment by antipsychotic drugs [1,49]. In addition, different

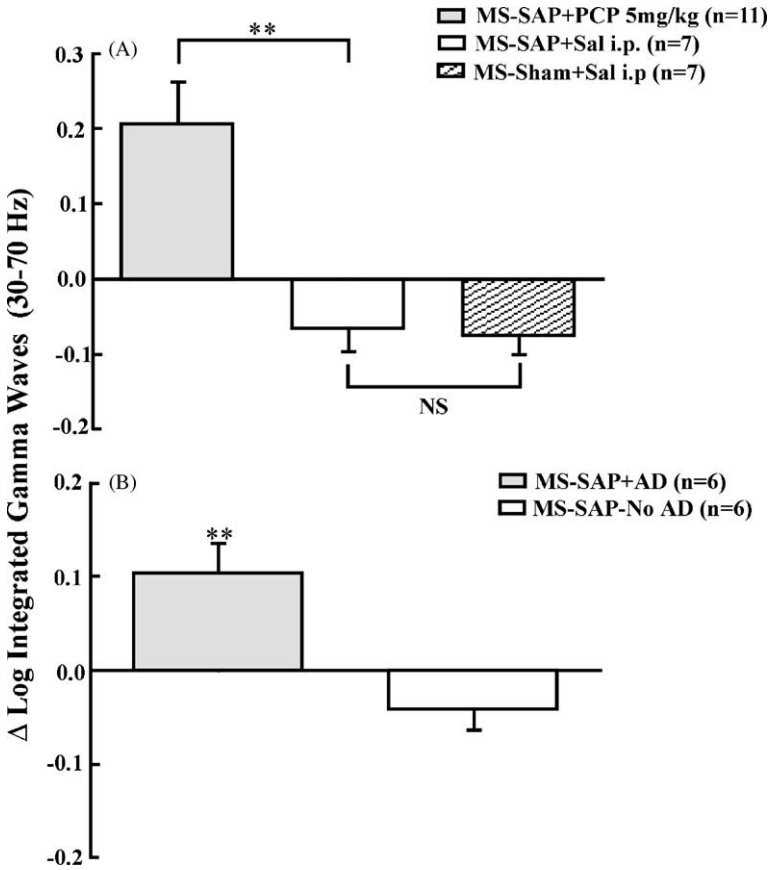

Fig. 9. Effect of cholinergic lesion of the medial septum on hippocampal gamma waves after PCP (A) or a hippocampal AD (B). $^{**}P < 0.01$, paired comparison (*t*-test). NS: not significant. *Abbreviations*: MS-Sham: medial septal sham lesion; MS-SAP: paramidline medial septal 192 IgG–saporin lesion.

psychotomimetic drugs were shown to selectively increase gamma EEG waves in humans [21]. The scalp EEG likely reflected an increase in gamma (fast) waves in the neocortex, and PCP appeared to increase gamma waves in both the neocortex and the hippocampus in rats [33].

In this study, we showed a correlation between high-amplitude hippocampal gamma waves and PPI impairment. PCP doses of 3 and 5 mg/kg i.p. significantly increased gamma waves (Fig. 1C) and disrupted PPI (Fig. 1B). The medial septal infusion of muscimol normalized the gamma waves induced by PCP (Figs. 2C and 5C) and normalized the PPI (Fig. 5B). However, a small decrease in gamma waves after injecting 0.25 μg of muscimol in the medial septum did not affect PPI. Thus, small changes (decrease or increase) of gamma waves in the hippocampus appear not to disrupt PPI, while high-amplitude gamma waves may disrupt PPI. A similar conclusion could be made concerning gamma waves (Fig. 7A) and PPI (Fig. 6B) induced by a hippocampal AD. Both gamma wave increase and PPI impairment occurred after an AD, and both measures were normalized if muscimol was injected into the medial septum before the AD. The hyperlocomotion after PCP or a hippocampal AD was also normalized by muscimol injected into the medial septum.

The septohippocampal system is only one of the several brain structures that contribute to PPI. In particular, PCP and hippocampal seizures are two conditions that induced PPI impairment through the hippocampus (discussed further; see also [39,40]). Some drugs, such as methamphetamine [40] and apomorphine [24,55] may mediate PPI impairment and hyperlocomotion by directly acting on the nucleus accumbens and not the hippocampus. During locomotion induced by methamphetamine, the hippocampal gamma (or theta) activity was not different than that during normal locomotion [40].

4.2. Control of normal and abnormal hippocampal electrical activity by the medial septum

Cholinergic and GABAergic afferents from the medial septum [2,25] control the theta and gamma rhythms of the hippocampus [8,9,12,32–35,39–41]. Midline injection of 192 IgG–saporin resulted in a strong attenuation of the hippocampal theta rhythm [29] but paramidline injections of 192 IgG–saporin only resulted in a small decrease of hippocampal theta [59]. These results were confirmed in our study. The larger suppression of hippocampal theta may relate to non-specific destruction of the medial sep-

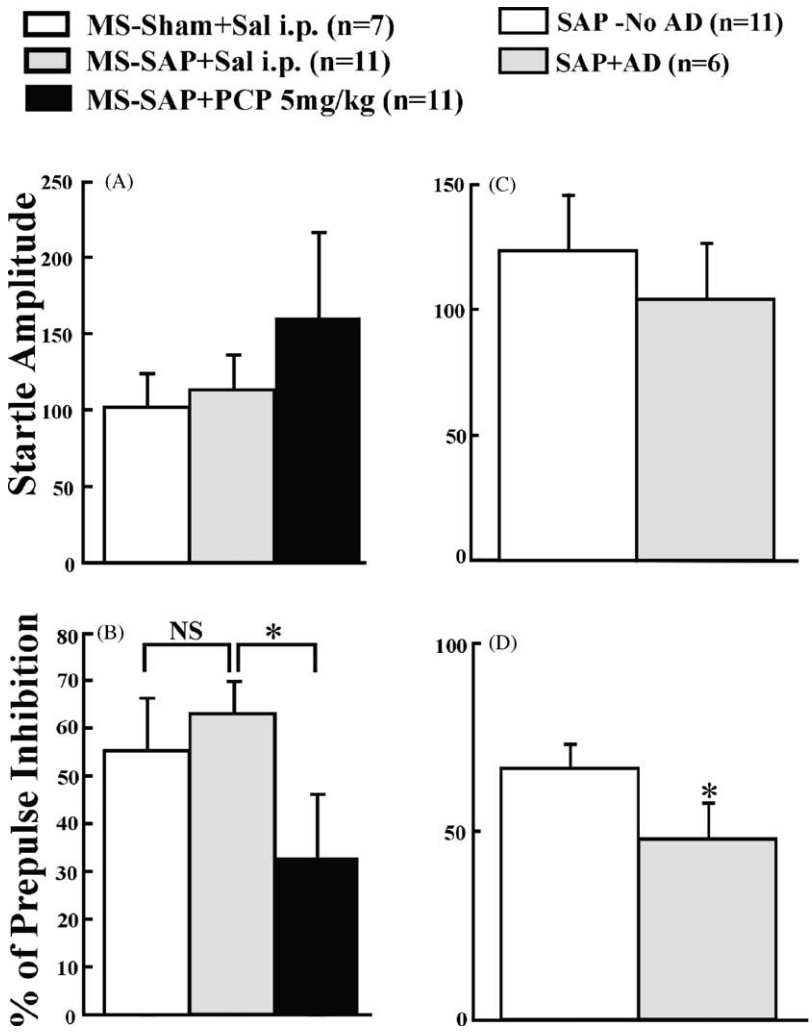

Fig. 10. Effect of cholinergic lesion of the medial septum on acoustic startle response (A and C) and prepulse inhibition following PCP (5 mg/kg i.p.) injections, calculated by integrated prepulse intensity (B and D). (A and B) Medial septal (MS) sham lesion vs. medial septal 192 IgG–saporin lesion (MS-SAP). (C and D) MS-SAP rats before and after a hippocampal AD. $^{*}P < 0.05$, paired *t*-test. NS: not significant.

tum, of both ChAT- and parvalbumin-containing (presumably GABAergic) neurons [25] (Table 1). However, unlike muscimol injection into the medial septum, neither midline nor paramidline 192 IgG–saporin lesion of the medial septum normalized the PPI impairment induced by PCP/hippocampal AD. In other words, the psychosis-like behaviors induced by PCP/hippocampal AD were observed after 192 IgG–saporin lesion of the medial septum, despite a strongly attenuated hippocampal theta. The spontaneous hippocampus gamma waves were apparently of normal amplitudes in 192 IgG–saporin lesion rats (present study; [29]) and the increase in gamma waves after PCP/hippocampal AD was similar to that in intact rats. This suggests that cholinergic septohippocampal neurons are not critical for generating the baseline gamma waves or the increase of hippocampal gamma waves after PCP/hippocampal AD. Similarly, hippocampal theta rhythm appears not to be essential for PPI impairment or gamma waves increase after PCP/hippocampal AD. In combination with the fact that muscimol injection into the medial septum normalized hippocampal gamma waves, hyperlocomotion, and PPI impairment, we suggest that GABAergic septohippocampal neurons may be responsible for the effects of muscimol injected into the medial septum.

Koch [26] showed that intrahippocampal injection of scopolamine attenuated the PPI disruption by kainic acid injection into the medial septum, and suggested the muscarinic cholinergic receptors in the hippocampus may control PPI. However, the latter finding did not necessarily suggest that septohippocampal cholinergic afferents mediated the PPI, since muscarinic receptor blockade may affect hippocampal neurons independent of septohippocampal cholinergic innervation.

4.3. Other structures mediating PPI impairment

A low dose of muscimol (0.01 μg in 1 μL) infused into the VP was shown to block the PPI deficit induced by injection

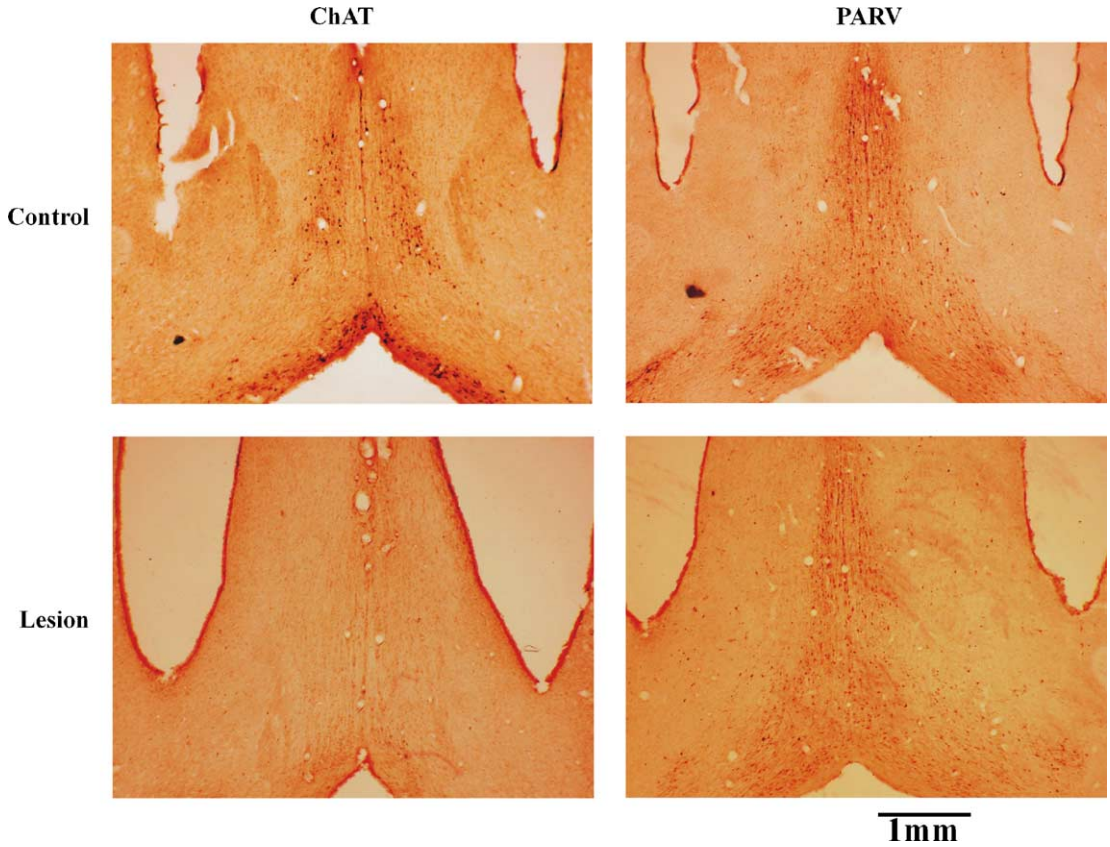

Fig. 11. Coronal sections of medial septal region stained for immunoreactivity to choline acetyltransferase (ChAT) or parvalbumin (PARV). Note the decrease of the ChAT-positive neurons in the section from a rat 21 days after bilateral paramidline injections of the medial septum of 0.14 μg/0.4 μL of 192 IgG–saporin as compared to saline (control) injection. Bar = 1 mm.

of dopamine into the nucleus accumbens [53]. This study raised two important issues: (1) whether the dose of muscimol (0.25 μg) in the medial septum was appropriate; and (2) whether diffusion of muscimol from the medial septum to the VP may mediate the PPI effects in this study. Concerning the first issue, our pilot studies indicated that doses of muscimol <0.25 μg did not have a significant effect on PCP-induced PPI deficit. Furthermore, Bland et al. reported that >0.5 μg of muscimol injected into the medial septum was necessary to suppress the hippocampal theta rhythm [9]. We found that a 0.25 μg dose of muscimol in the medial septum affected behavior (like PPI) and hippocampal gamma waves but not the hippocampal theta rhythm. While it is difficult to definitely rule out the participation of the VP in PPI in this study, we believe that the role of the VP may be limited for three reasons. First, much of the VP structure was >2 mm from the medial septal injection sites, and diffusion of 0.4–1 μL of muscimol was shown to be <2 mm using a behavioral outcome or field potential recordings [41] or by using autoradiography [42]. Second, we showed that direct injections of muscimol (0.1 μg/0.5 μL) into the VP did not have a marked effect on PPI deficit induced by PCP (2 rats) or a hippocampal AD (two rats). Third, Kretschmer and Koch [28] demonstrated that the VP did not mediate the PPI disruption induced by NMDA receptor antagonists, and PCP exerted its psychosis-like effects by blocking NMDA receptors [22]. Thus, we suggest that the main target of muscimol was in the medial septum.

4.4. Septohippocampal system and psychotic behaviors

There have been various studies that implicated the involvement of the hippocampus in psychosis-like behaviors. Pathology in the hippocampus [3,6,16] has been found in post-mortem brains of schizophrenic patients but not controls. Stimulation of the septum or the hippocampus in humans induced psychiatric symptoms such as hallucinations and emotional changes [15,17], while functional imaging studies indicate that an activated hippocampus was associated with the experience of positive symptoms of schizophrenia [18,48,49]. Chemical stimulation of the septohippocampal system has been shown to affect PPI [5,13,28,56], and neurons in the medial septum and the hippocampus appeared to be involved in the gating of auditory signals [7,44].

At the doses used in our study, PCP binds to the hippocampus through sigma or NMDA receptors [22,51] and alters hippocampal field potentials [14,46,47,52] and single-unit activities [46]. Hippocampal gamma activity is likely generated by a network of GABAergic interneurons [58]

interacting with pyramidal cells [35]. Increased gamma waves may reflect the alteration of the hippocampal circuit by a hippocampal AD or by PCP blocking NMDA receptors [14]. Hippocampal (glutamatergic) afferents to the nucleus accumbens [19] or indirectly to the ventral tegmental area [30,31] may drive the release of dopamine in the nucleus accumbens [11,30,31]. Locomotor hyperactivity and PPI impairment may result from bombardment of the nucleus accumbens and other areas by abnormal hippocampal activity [5,24,38,43,53].

Normalization of the hippocampal gamma rhythm by manipulation of the medial septum offers a new method to suppress behavioral abnormalities induced by PCP. PCP-induced deficit in PPI was not reversed by a typical antipsychotic/dopamine antagonist [23], but it was reversed by an atypical antipsychotic clozapine [4]. Clozapine may suppress psychotic symptoms by blocking 5HT-2A receptors on septohippocampal GABAergic neurons [37]. In the present study, a single dose of muscimol (0.25 μg) in the medial septum had no apparent effect on normal behaviors but suppressed the psychosis-like behaviors induced by PCP and a hippocampal AD. Thus, control of neural activities at the medial septum may offer an alternative treatment for symptoms of schizophrenia.

Acknowledgements

This study was supported by a NSERC grant and CIHR grant MOP-15685 to L.S. Leung. J. Ma was partially supported by a postdoctoral fellowship from the Ontario Mental Health Foundation. We thank P. Peloquin for reading this manuscript.

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