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Hippocampal Modulation of Acoustic Startle and Prepulse Inhibition in the Rat

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CAINE, S. B., M. A. GEYER AND N. R. SWERDLOW. *Hippocampal modulation of acoustic startle and prepulse inhibition in the rat.* PHARMACOL BIOCHEM BEHAV 43(4) 1201-1208, 1992.—Prepulse inhibition (PPI) is the normal reduction in a startle response that occurs when the startling stimulus is preceded by a weak lead stimulus ("prepulse"). Schizophrenic patients exhibit abnormally low levels of PPI; therefore, animal models of deficient PPI may provide information regarding neural dysfunctions underlying schizophrenia. We recently reported that infusion of the cholinergic agonist carbachol into the dentate gyrus (DG) disrupts PPI in the rat. We now report the effects of carbachol microinjected into CA1, the DG, or the ventral subiculum (VS) on acoustic startle and PPI. Carbachol infusion into CA1 or the DG depressed startle. Carbachol infusion decreased PPI with a regional rank-order potency CA1 > DG > VS. CA1 infusions more potently depressed the startle reflex. By contrast, DG infusions preferentially decreased PPI, while VS infusions decreased PPI without altering startle amplitude. Coinfusion with the muscarinic cholinergic antagonist atropine opposed the effects of carbachol. These results demonstrate the regional heterogeneity and pharmacological specificity of the hippocampal cholinergic modulation of acoustic startle and PPI and suggest that abnormalities within various regions of the hippocampal formation may contribute to deficient sensorimotor gating in schizophrenic patients.

Prepulse inhibition Sensorimotor gating Startle Hippocampus Schizophrenia
Dentate gyrus CA1 Subiculum Carbachol Acetylcholine

PREPULSE inhibition (PPI) of the startle reflex is a measure of sensorimotor gating that can be studied in both humans and animals (6,14,33). Schizophrenic patients exhibit deficient sensorimotor gating as measured by PPI (7,8,15); therefore, studies of the neural substrates of PPI may yield information regarding neural systems involved in schizophrenic pathophysiology. We previously reported that infusion of the cholinergic agonist carbachol into the dentate gyrus (DG) of the hippocampal formation decreases PPI in rats (10), suggesting that the hippocampal formation may play a role in deficient sensorimotor gating in schizophrenic patients. Thus, carbachol infusion into the dentate gyrus, but not the overlying parietal cortex, decreased PPI, an effect that was not reversed by systemic pretreatment with the neuroleptic agent spiperone. However, the relative contributions of hippocampal substructures in the modulation of PPI are unknown. Further, it remains to be demonstrated whether the effects of intrahippocampal carbachol on PPI are mediated via a pharmacologically distinct action at nicotinic or muscarinic cholinergic receptors.

The present experiments were designed to further assess the anatomic, pharmacological, and behavioral specificity of the hippocampal cholinergic modulation of PPI. Experiment 1 evaluated the effects of carbachol microinjected into CA1, the DG, or the ventral subiculum (VS) on the acoustic startle reflex and PPI. Experiments 2 and 3 determined the effects of intrahippocampal microinjections of atropine, either alone or in combination with carbachol, on acoustic startle and PPI.

METHOD

Subjects

Forty male Sprague-Dawley rats (225-250 g; Harlan, Indianapolis, IN) were housed in pairs and maintained on a reversed 12 L : 12 D schedule (lights off at 0700 h) with food and water provided ad lib. Testing occurred during the dark phase, between 0900 and 1500 h. Animals were handled within 3 days of arrival and daily thereafter.

Chemicals

Carbamycholine HCl (carbachol) was obtained from Sigma Chemical Co. (St. Louis, MO). Atropine sulfate was obtained from Burroughs Wellcome Co. (Research Triangle Park, NC). Both compounds were dissolved in saline.

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Cannulations

Animals were anesthetized and placed in a Kopf (Tujunga, CA) stereotaxic instrument with the toothbar set level with the interaural line. Stainless steel 23-ga cannulae were implanted bilaterally 1.5 mm above the DG (AP −3.6 from bregma, L ± 2.0, DV −3.0 from skull), 3.0 mm above the ventral CA1 region (AP −5.2 from bregma, L ± 5.8, DV −5.0 from skull), or 3.0 mm above the VS (AP −6.5 from bregma, L ± 5.0, DV −5.0 from skull) of the hippocampal formation. Cannulae were embedded in light-cured Sun Schein filled resin (Henry Schein, Port Washington, NY), anchored with four skull screws, and filled with removable stylet wire.

Infusions

Infusions were made by replacing the wire stylets with 30-ga needles fashioned to extend 1.5 mm (DG) or 3.0 mm (CA1, VS) beyond the end of the cannulae. Infusions were delivered bilaterally in a volume of 0.5 μl/side over a period of 42 s using a Hamilton microsyringe (Hamilton Co., Reno, NV) connected to the needle via polyethylene tubing. The needle was left in place for 30 s after infusion to allow for the solution to diffuse away from the injection site. The needle was then replaced with a wire stylet. Previous studies demonstrated that infusion of carbachol into the overlying neocortex less than 2 mm dorsal from the DG had no effect on PPI, in contrast to infusions into the DG, suggesting that carbachol infusions into the hippocampus have a localized effect (10).

Apparatus

Four startle chambers (SR-LAB, San Diego Instruments, San Diego, CA) were used, each consisting of a Plexiglas cylinder 8.2 cm in diameter, resting on a Plexiglas frame within a ventilated enclosure. Acoustic noise bursts were presented via a loudspeaker mounted 24 cm above the animal. A piezoelectric accelerometer (assembled using a Blatek Audio Transducer Model 6030, Blatek Inc., State College, PA) mounted below the Plexiglas frame detected and transduced motion within the cylinder. Stabilimeter readings were rectified and recorded by a microcomputer and interface assembly (San Diego Instruments), with 100 1-ms readings collected beginning at the stimulus onset. Startle amplitude was defined as the average of the 100 readings.

Test Session

The test session in all experiments consisted of two consecutive blocks of 25 test trials each (50 trials total) with an average of 15 s separating trials. A 65-dB background noise was constant throughout the entire test session. After a 5-min acclimation period in the test chamber, five different trial types were delivered in pseudorandom order: startle stimulus alone [a 118-dB (A) 40-ms broad band burst], no stimulation, or startle stimulus preceded 60, 120, or 500 ms earlier by a prepulse [an 80-dB (A) 20-ms broad band burst, pp60, pp120, or pp500, respectively].

Histology

After completion of the experiments, animals were euthanized by IP injection with pentobarbital sodium (100 mg/kg) followed by intracardiac infusion with 50 ml 10% formalin. Brains were removed and cannulae placements verified histologically.

Experiment 1

Thirty-three experimentally naive animals were fitted with hippocampal cannulae for infusions into the DG (n = 10), VS (n = 10), or CA1 (n = 13). Starting 1 week after surgery, animals were tested in the startle session four times, with 4 days between sessions. Immediately prior to a session, each animal received a bilateral infusion of 0, 0.1, 0.2, or 0.4 μg carbachol/side. These doses have been shown to be in the low-dose range for intradentate carbachol-induced disruption of PPI (10). Every animal received each dose once, with the order of dose counterbalanced across sessions using a Latin square design. Two animals with CA1 cannulae were deleted from the study due to behavioral evidence of seizures after infusion of the highest dose of carbachol.

Experiment 2

Seven experimentally naive animals were fitted with cannulae for infusions into the dentate gyrus. Starting 1 week later, animals were tested in the startle session four times, with 4 days separating tests. Immediately prior to a session, each animal received a bilateral infusion of 0, 0.2, 0.4, or 0.8 μg atropine/side. Every animal received each dose once, with the order of doses counterbalanced across sessions. One animal was deleted from the data analysis due to an unstable cannula.

Experiment 3

One week after completion of Experiment 1, 26 of the same animals were tested in the startle session two more times, with 4 days between sessions. Five of the animals from Experiment 1 were exempted from further studies due to unstable or blocked cannulae. Immediately prior to a session, each animal received a bilateral infusion of 0.4 μg carbachol/side or a combination of 0.4 μg carbachol with 0.4 μg atropine/side. Every animal received each treatment once, with the order of dose counterbalanced across sessions. Two animals were deleted from the data analysis due to behavioral evidence of seizures.

Data Analysis

Startle amplitude was analyzed using analysis of variance (ANOVA) with repeated measures on dose (carbachol in Experiment 1, atropine in Experiments 2 and 3) and block. The amount of PPI is expressed as the percentage decrease in the startle response caused by presentation of the prepulse, and was calculated using the following equation:

[(startle amplitude caused by pulse alone −
startle amplitude caused by pulse preceded by prepulse)/
startle amplitude caused by pulse alone] × 100.

Using this description of PPI, a high degree of sensorimotor gating is reflected in a high "% PPI" value while less or no gating results in a small or negative % PPI value. The ED_{50} for carbachol's effects on acoustic startle and PPI were determined using a computer program based upon the following equation:

$$Y = B + (A - B) * \exp\{[-X * \mathrm{LOG}(2)]/C\},$$

where A = control response, B = maximal response, and C = ED_{50}. PPI was analyzed using ANOVA with repeated measures on dose, block, and prepulse interval. Alpha was 0.05

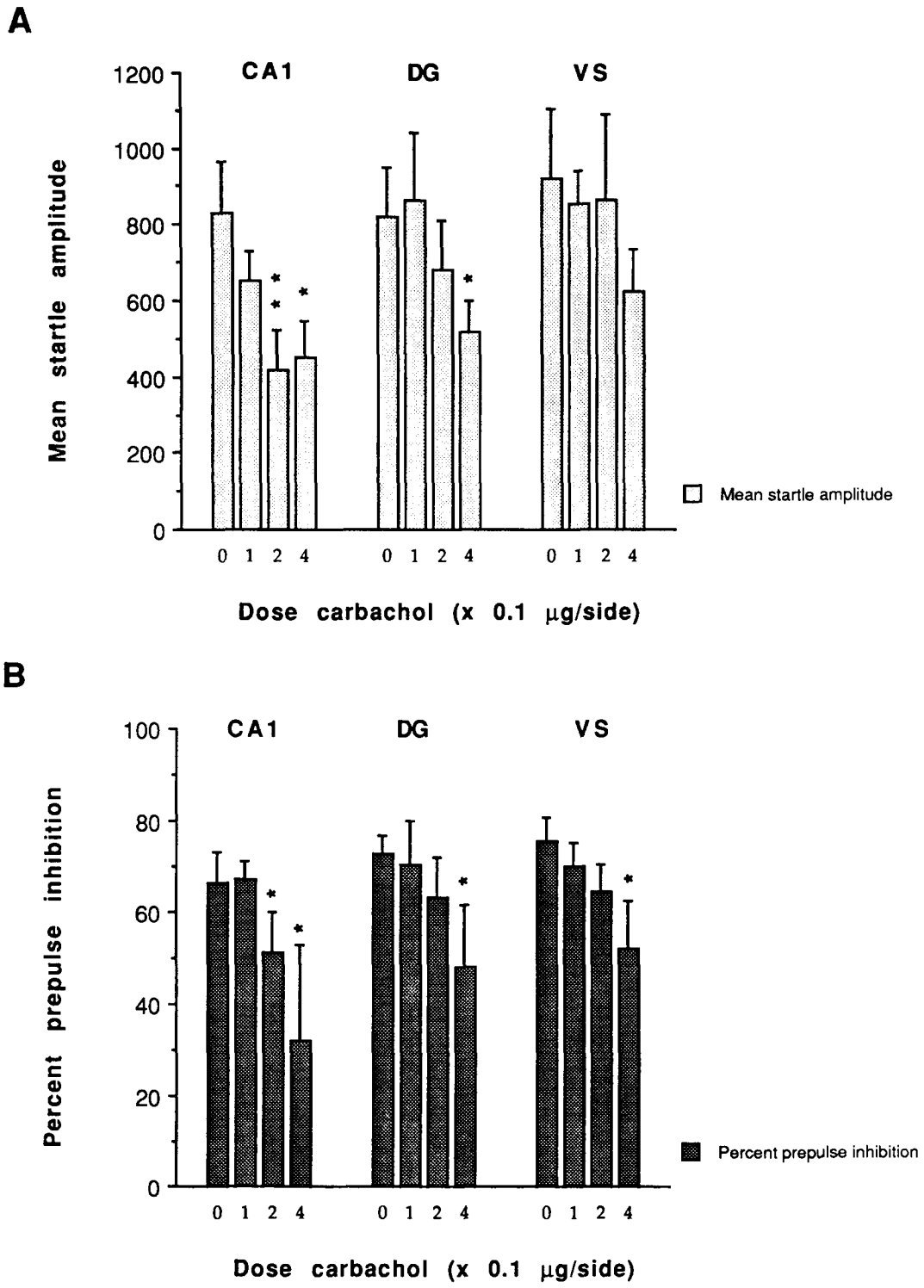

FIG. 1. Effects of carbachol infusion into CA1, the dentate gyrus (DG) or the ventral subiculum (VS) on (A) startle reactivity and (B) prepulse inhibition of the startle reflex. Bilateral infusions were completed over a period of 42 s in a volume of 0.5 µl/side. For clarity, startle data are presented for both blocks combined and PPI data for all prepulse intervals in both blocks combined. Error bars indicate SEM, and asterisks indicate level of significance (*$p < 0.05$, **$p < 0.01$) by posthoc individual comparisons following significant main effect of dose by overall ANOVA.

TABLE 1

REGIONAL POTENCY OF CARBACHOL TO ALTER STARTLE AND PPI

ED_{50} (μg/side)	Dentate Gyrus	Ventral Subiculum	CA1
Depression of startle reflex	>0.5	NS	0.16
Decrease in PPI	0.27	0.42	0.23

for all new experiments; α for the replication of previous experiments (10) was 0.1.

RESULTS

Experiment 1: Carbachol Infusion Into CA1 and the DG Depressed Startle and Carbachol Infusion Decreased PPI With a Rank-Order Potency CA1 > DG > VS

The effects of carbachol infused into the hippocampus on the acoustic startle reflex for both blocks are presented in Fig. 1A. Carbachol depressed startle amplitude when infused into CA1, $F(3, 30) = 4.94, p < 0.01$, or the DG, $F(3, 27) = 4.21$, $p < 0.01$, but not the VS, $F(3, 27) = 1.00$, NS. Analysis of data from CA1 and VS experiments also revealed a significant effect of block on startle amplitude. Individual comparisons revealed that bilateral infusions of 0.2 μg, $F(1, 10) = 10.33$, $p < 0.01$, or 0.4 μg, $F(1, 10) = 7.06$, $p < 0.05$, carbachol into CA1 depressed startle. In contrast, only the highest dose of carbachol infused into the DG depressed startle, $F(1, 9) = 8.80, p < 0.05$.

The effects of carbachol infused into the hippocampus on PPI are presented in Fig. 1B. Carbachol decreased PPI when infused into CA1, $F(3, 30) = 4.46$, $p < 0.01$, the DG, $F(3, 27) = 2.78$, $p < 0.1$, or the VS, $F(3, 27) = 3.76$, $p < 0.05$. There were also significant main effects of prepulse interval (DG, VS) and a drug × prepulse interval interaction (CA1). Individual comparisons revealed that 0.2 μg, $F(1, 10) = 6.05$, $p < 0.05$, or 0.4 μg, $F(1, 10) = 5.85$, $p < 0.05$, of carbachol infused into CA1 decreased PPI, but only the highest dose of carbachol decreased PPI in the DG, $F(1, 9) = 5.56$, $p < 0.05$, or VS, $F(1, 9) = 4.92, p < 0.05$.

To compare the relative regional potency of carbachol to alter the startle reflex and PPI, we calculated the ED_{50} for carbachol's effects on acoustic startle or PPI in CA1, the DG, or the VS. The ED_{50} for the regional effects of carbachol on acoustic startle and PPI are shown in Table 1. CA1 infusions more potently decreased acoustic startle, while DG infusions more potently disrupted PPI; VS infusions decreased PPI without significantly altering startle amplitude.

Experiment 2: Atropine Infusion Into the DG Had no Affect on the Startle Reflex or PPI

The effects of atropine infused into the DG on acoustic startle and PPI for all blocks and prepulse intervals are shown in Fig. 2. Intradentate atropine did not significantly alter startle amplitude, $F(3, 15) = 0.26$, NS; there was a significant main effect of block, $F(1, 5) = 34.44, p < 0.01$. Intradentate atropine also did not significantly alter PPI, $F(3, 15) = 0.29$, NS; there was a significant main effect of prepulse interval, $F(2, 10) = 16.46, p < 0.001$.

Experiment 3: Effects of Intrahippocampal Carbachol on Acoustic Startle and PPI are Opposed by Coinfusion With Atropine

The effects of atropine coinfused with carbachol into CA1, the DG, and the VS on the startle reflex for both blocks are shown in Fig. 3A. A significant main effect of dose (atropine) for all infusions (CA1, DG, VS) indicated that coinfusion of atropine with carbachol significantly increased startle amplitude compared with the carbachol-alone condition, $F(1, 21) = 4.40, p < 0.05$; there was no dose × site (CA1, DG, VS) interaction, $F(2, 21) = 0.48$, NS.

The effects of atropine coinfused with carbachol into CA1, the DG, and the VS on PPI are shown in Fig. 3. A significant main effect of dose (atropine) for all infusions indicated that coinfusion of atropine with carbachol significantly increased PPI compared with the carbachol-alone condition, $F(1, 21) = 9.41, p < 0.01$; there was no dose × site (CA1, DG, VS) interaction, $F(2, 21) = 0.98$, NS.

Histology

Histological verifications of the site of infusions for all experiments are diagrammed in Fig. 4.

DISCUSSION

We report here that carbachol infusion into CA1, the DG, or the VS disrupts sensorimotor gating of startle, but there is some regional heterogeneity of the effects of intrahippocampal carbachol. Carbachol infusion into CA1 more potently depresses the acoustic startle reflex, while intradentate carbachol preferentially decreases PPI. Infusion into the VS disrupts PPI without significantly altering startle amplitude. The effects of carbachol appear to be mediated by muscarinic cholinergic receptors because coinfusion of atropine opposes the effects of carbachol on acoustic startle and PPI. Intrahippocampal infusion of atropine alone does not significantly alter these behaviors.

The disruption of PPI following intrahippocampal carbachol is dissociated from alterations in the startle reflex. We previously demonstrated that doses of intradentate carbachol that do not alter startle reactivity significantly disrupt PPI (10), similar to the findings here with carbachol infusions into the VS. The ED_{50} for carbachol's effects on startle and PPI suggest that the DG and VS may modulate sensorimotor gating more potently than they modulate startle amplitude; carbachol infusion into CA1, however, more potently alters startle amplitude than PPI. These findings are consistent with several other reports that PPI and startle reactivity are mediated by dissociable pharmacological and anatomic substrates (14,17,28,30,31,34). This dissociation is also evident in psychiatric patients who exhibit impaired PPI but normal startle reactivity, including patients with schizophrenia (7,8,15) and Huntington's disease (see 29).

The regional potency of carbachol to alter startle or PPI in this study (CA1 > DG > VS) may relate to the afferent innervation of these structures. The cholinergic input to the hippocampal formation arises primarily from the medial septum/diagonal band nuclei (22), which innervate primarily the supra- and infragranular regions of the DG, stratum oriens and stratum radiatum of the hippocampus, and subiculum (13,20). Cholinergic nerve terminals are more highly concentrated in the DG and CA1 than the VS (21), and cholinergic receptors are approximately two fold greater in the DG and CA1 relative to the VS (24). This correlates well with the two

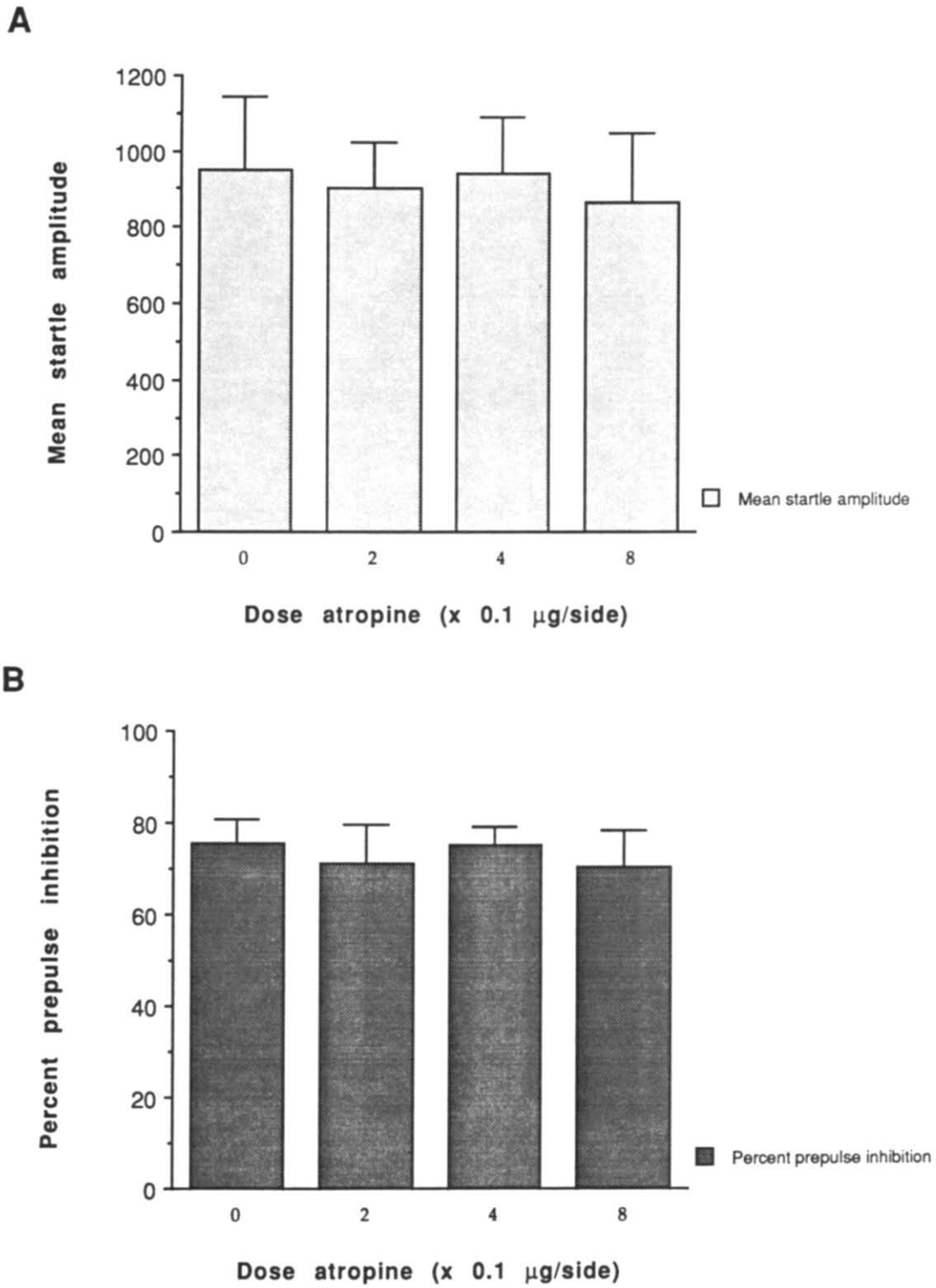

FIG. 2. Effects of atropine infusion into the dentate gyrus on (A) startle reactivity and (B) prepulse inhibition of the startle reflex. Refer to Fig. 1 for further details.

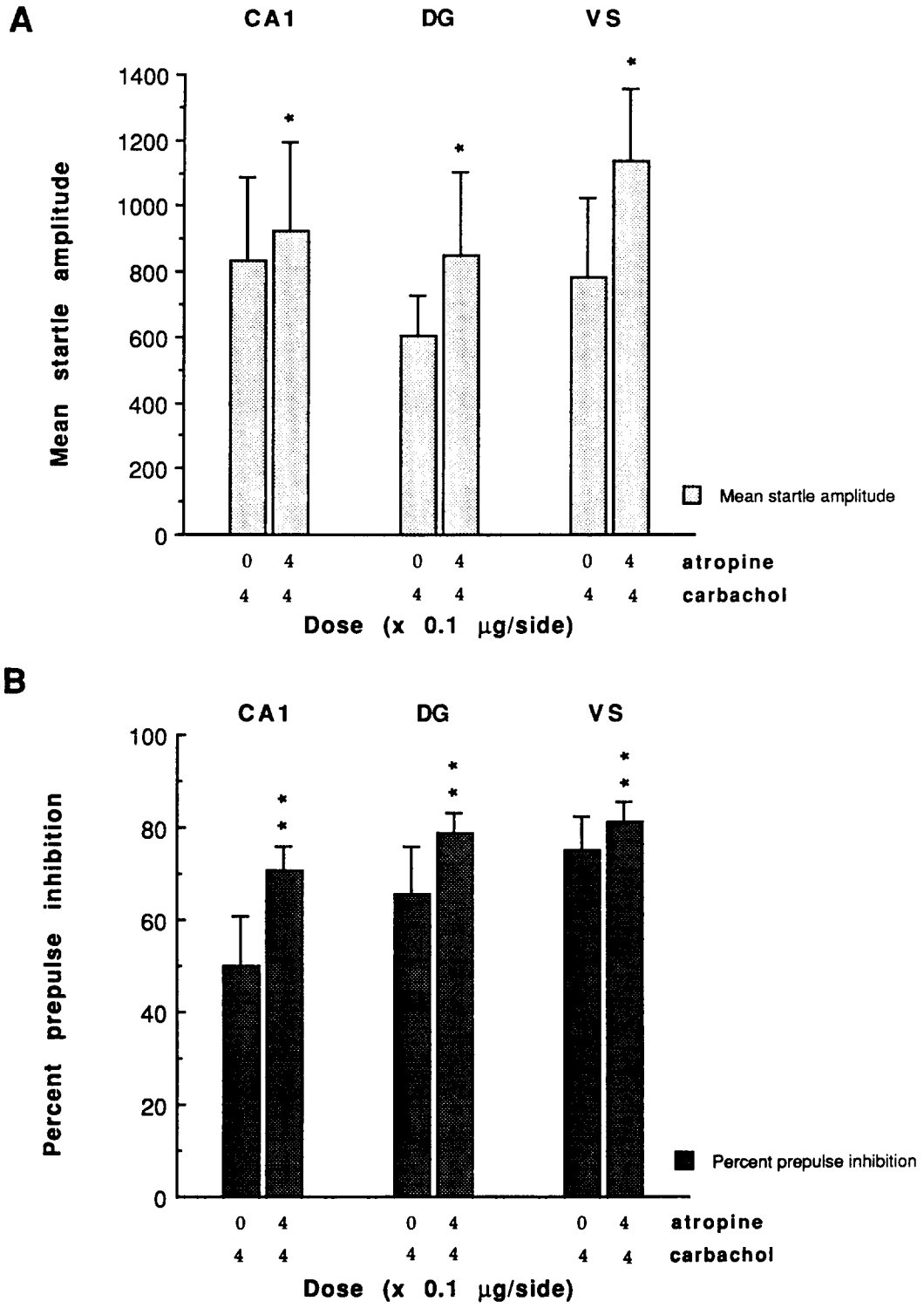

FIG. 3. Effects of coinfusion of atropine with carbachol on (A) startle reactivity and (B) prepulse inhibition of the startle reflex. Asterisks indicate significant main effect of dose of atropine (*$p < 0.05$, **$p < 0.01$) by overall ANOVA.

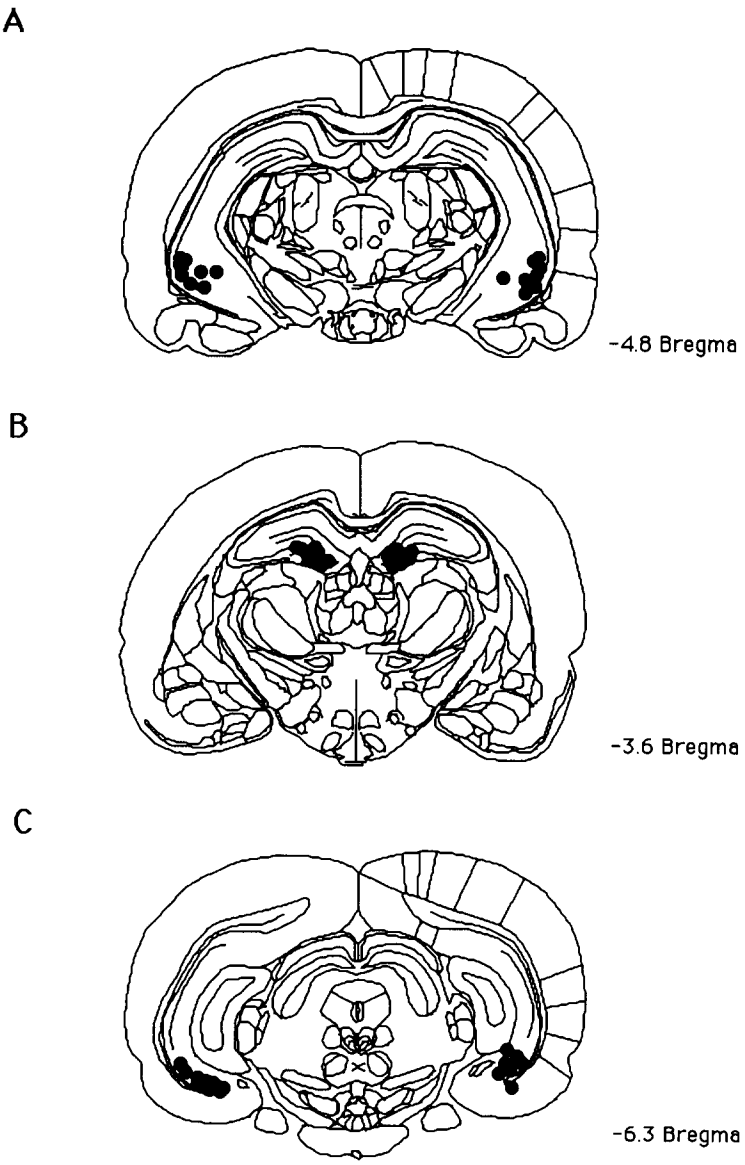

FIG. 4. Sites of bilateral infusions aimed at (A) CA1, (B) the dentate gyrus (DG) or (C), the ventral subiculum (VS) for all experiments (± 0.5 mm in coronal plane).

fold higher potency of DG and CA1 infusions to disrupt PPI compared to VS infusions in this study. Other behavioral studies have also observed that carbachol is more potent when infused into the dorsal hippocampus than when infused into the ventral hippocampus (18).

The present findings demonstrate that carbachol infusion into various hippocampal substructures disrupts PPI with a regional, pharmacological, and behavioral specificity. The hippocampal modulation of sensorimotor gating may be relevant to the pathophysiology of schizophrenia. Early findings of decreased PPI in schizophrenic patients (8) have now been replicated with larger, carefully controlled studies (7,15), and deficient sensory gating in schizophrenic patients has also been demonstrated using electroencephalographic measures (1,23). Abnormalities within the hippocampal formation of schizophrenic patients have been noted in volumetric, morphological, and metabolic studies (2-5,9,11,12,16,19,25,26). While our present findings support the notion that abnormalities in hippocampal function may contribute to deficient sensorimotor gating in schizophrenic patients, it is likely that such gating deficits arise from several different substrates that converge within a common interconnected circuitry linking subcortical and cortical elements of the limbic system (27,29,32).

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