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Accumbens D_2 Modulation of Sensorimotor Gating in Rats: Assessing Anatomical Localization

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WAN, F. J., M. A. GEYER AND N. R. SWERDLOW. *Accumbens D_2 modulation of sensorimotor gating in rats: Assessing anatomical localization.* PHARMACOL BIOCHEM BEHAV 49(1) 155–163, 1994. – The normal reduction in acoustic startle amplitude caused by a weak prepulse (prepulse inhibition; PPI) is deficient in schizophrenic patients and in rats after systemic or intraaccumbens treatment with the D_2 dopamine agonist quinpirole. We examined the anatomical substrates of the PPI-disruptive effects of intraaccumbens quinpirole. PPI was significantly reduced in a dose-dependent manner by quinpirole infusion into the medial accumbens shell region, the lateral accumbens core region, and an intermediate central region. There was a weak tendency for this quinpirole effect to be more pronounced in core and central accumbens regions than in the medial and anteromedial accumbens. Using the retrograde tracer Nuclear yellow, shell and core regions were verified to receive different patterns of limbic cortical innervation. Although the accumbens appears to have a complex and functionally diversified intrinsic anatomy, the accumbens D_2 modulation of sensorimotor gating appears to be distributed across several different accumbens subregions.

Nucleus accumbens Quinpirole Schizophrenia Sensorimotor gating Startle

THE acoustic startle reflex is normally inhibited when the startling stimulus is preceded 30–500 ms by a weak prepulse. Prepulse inhibition (PPI) can be measured automatically in humans and rats, and is significantly reduced in humans with certain neuropsychiatric disorders (19,20,23) and in rats after manipulations of the hippocampus (4), ventral striatum (22,26, 28), ventral pallidum (21), or pontine reticular formation (25). Because PPI is significantly reduced in patients with schizophrenia (2,8), and in rats after ventral striatal D_2 dopamine (DA) receptor activation (28), this measure might provide useful information regarding the pathophysiology of DA-mediated abnormalities of sensorimotor gating in schizophrenia (13,23,27).

Five distinct DA receptor subtypes in the brain have been identified, and were divided into two subfamilies, D_1 and D_2, on the basis of ligand binding pharmacology and amino acid homology. The D_2 subfamily is composed of the D_2, D_3 and D_4 subtypes. The nucleus accumbens (NAC) appears to be one anatomical locus of the D_2 subfamily modulation of PPI. Direct microinfusion of the D_2 subfamily agonist quinpirole (D_2/D_3) into the NAC causes a dose-dependent disruption of PPI, which is then prevented by pretreatment with D_2 subfamily antagonist haloperidol (17,28). An abundance of evidence suggests that the NAC is an anatomically heterogeneous structure with medial shell and lateral core regions supporting distinct afferent (10) and efferent projections (30), and perhaps serving different behavioral functions (7,18). In our initial report of an accumbens D_2 modulation of PPI, we observed that the most potent reduction in PPI after intraaccumbens quinpriole infusion occurred after infusions into the lateral accumbens core region (28). If the D_2 modulation of PPI is localized within specific accumbens subregions, this would suggest that specific accumbens D_2 interactions with limbic inputs critically regulate sensorimotor gating, and may be substrates for deficient sensorimotor gating in schizophrenia. In the present study, we assessed PPI after quinpirole infusion into separate accumbens subregions and verified the different limbic afferents of these accumbens subregions by fluorescent retrograde tracer.

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GENERAL METHOD

Seventy-two male Sprague-Dawley rats (225–250 g) were housed in groups of two to three and maintained on a reversed 12 L : 12 D schedule (lights off at 0700 h) with food and water provided continously. Behavior testing occured between 0900 and 1500 h, during the dark phase, when acoustic startle is most robust and least variable (6). Animals were handled individually within 3 days of arrival, and daily thereafter. All surgery occured between 7 and 14 days after arrival, using pentobarbital sodium anesthesia (50 mg/kg) and a Kopf stereotaxic instrument. Bilateral intra-NAC 23 ga cannulae were aimed 3 mm above four separate coordinates within the NAC according to a stereotaxic atlas (16): lateral, AP +1.0, L ±2.3, DV −7.0 (n = 16); central, AP +1.2, L ±1.7, DV −7.0 (n = 9); medial, AP +1.2, L ±0.8, DV −7.2 (n = 9); anteromedial, AP +1.7, L ±0.8, DV −7.2 (n = 8). Cannulae were anchored to the skull with cement and screws, and filled with wire stylets.

Each of four startle chambers (SR-LAB, San Diego Instruments, San Diego, CA) were 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 amplitide 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 sensitivites 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.

Testing began 7–10 days after surgery, and included four separate test sessions separated by 4 days. Immediately prior to a session, stylet wires were removed from the intracerebral cannulae and replaced by a 30 ga needle. All rats received bilateral intra-NAC infusion of one of four quinpirole doses (0, 0.1, 1.0, or 10.0 μg in 0.5 μl/72 s) in each session, with dose order balanced among rats for all tests. 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 four types of stimuli: a startle pulse [P-ALONE: a 118-dB(A) 40-ms broad band burst] and three 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. The session was designed with five trial types: P-ALONE, each of the three prepulse trials followed by 10 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 intertrial interval averaged 15 s.

In order to control for the potentially confounding effects of repeated intracerebral drug infusion and startle testing, this experiment was repeated in experimentally naive rats that were fitted with intra-NAC cannulae directed towards lateral (n = 13), medial (n = 9), and anteromedial (n = 8) NAC regions, coordinates as above. Each rat received bilateral intra-NAC infusion of either 0 or 10 μg quinpirole in two sessions separated by 4 days with balanced dose order. Infusion volume was reduced to 0.25 μl/81 s to further enhance anatomical specificity of the drug injections. Rats were assigned to dose groups based on matched startle amplitude during a brief pretest session 7 days postsurgery to further reduce intergroup variability. Test sessions were as described above.

After completion of behavioral testing, all animals were sacrified by a lethal overdose of pentobarbital followed by intracardiac perfusion of 10% formalin/saline. Brains were then removed and cannula placements were verified histologically. A separate group of rats received intra-NAC infusions of Nuclear yellow (2.5%, 0.5 μl) into medial or lateral NAC regions, coordinates as above. These rats were sacrified by a lethal overdose of pentobarbital followed by intracardiac perfusion of a 1% formalin solution 2–6 days later, and 40 μm brain sections were cut and mounted on segregated slides for either cresyl violet staining or fluorescent microscopy of adjacent brain sections. Injection sites and regions of retrograde labeling were recorded and photographed. Behavioral data were analyzed using mixed design ANOVAs. Alpha was 0.05.

RESULTS

The effects of intra-NAC infusion of quinpirole on startle amplitude and PPI are seen in Figs. 1 and 2. A two-way ANOVA using region (four regions in the NAC) as a between-subject factor and dose as the within-subject factor revealed no significant effect of quinpirole on P-ALONE amplitude, $F(3, 114) = 2.54$, NS, no significant effect of region, $F(3, 78) = 1.71$, NS, and no significant interaction of quinpirole × region, $F(9, 114) = 1.52$, NS. Inspection of the data (Fig. 1), however, suggested that quinpirole infusion into the lateral NAC and medial NAC tended to increase startle amplitude. This was verified by independent ANOVAs (effect of quinpirole in lateral NAC: $F(3, 45) = 3.37, p < 0.03$; effect of quinpirole in medial NAC: $F(3, 24) = 3.21, p < 0.05$).

As previously reported (28), intra-NAC quinpirole infusion resulted in a dose-dependent reduction in PPI (Fig. 2). A two-way ANOVA using region (four regions in the NAC) as a between-subject factor and dose and prepulse type as within-subject factors revealed a significant effect of drug, $F(3, 114) = 11.53, p < 0.0005$, and a significant effect of prepulse type, $F(2, 76) = 25.20, p < 0.0005$, but no significant effect of region, or the interactions of drug × region ($F < 1$ both comparisons) or drug × region × prepulse type, $F(18, 228) = 1.22$, NS. Independent ANOVAs with repeated measures on dose were performed for each of the four individual NAC regions. This analysis revealed a significant effect of drug in the lateral, $F(3, 45) = 8.30, p < 0.0005$, and central, $F(3, 24) = 2.31, p = 0.04$, accumbens regions, but not in either the medial, $F(3, 24) = 2.31$, NS, or anteromedial, $F(3, 21) = 2.45$, NS, regions.

There was no consistent relationship between the effects of quinpirole on P-ALONE amplitude and PPI in this study. For example, quinpirole significantly reduced PPI without significant changes in P-ALONE amplitude after infusion into the central NAC, while reduced PPI after quinpirole infusion into the lateral NAC was accompanied by significantly elevated P-ALONE amplitudes. A similar dissociation between drug-induced changes in P-ALONE and PPI has been reported

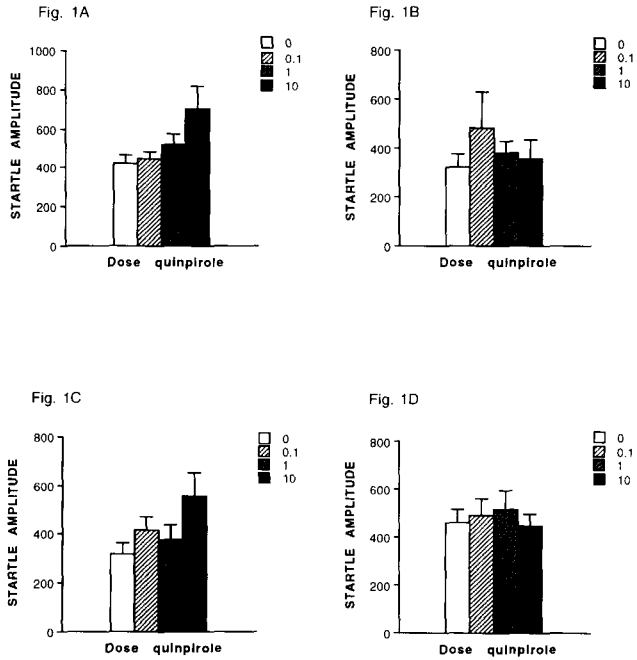

FIG. 1. Mean startle amplitude after infusion of quinpirole (0, 0.1, 1, 10 μg) into four separate regions of the NAC: (A) lateral NAC, (B) central NAC, (C) medial NAC, (D) anteromedial NAC (coordinates in text). Overall two-way ANOVA revealed no significant effect of quinpirole or region, and no significant quinpirole × region interaction ($p > 0.05$, all comparisons).

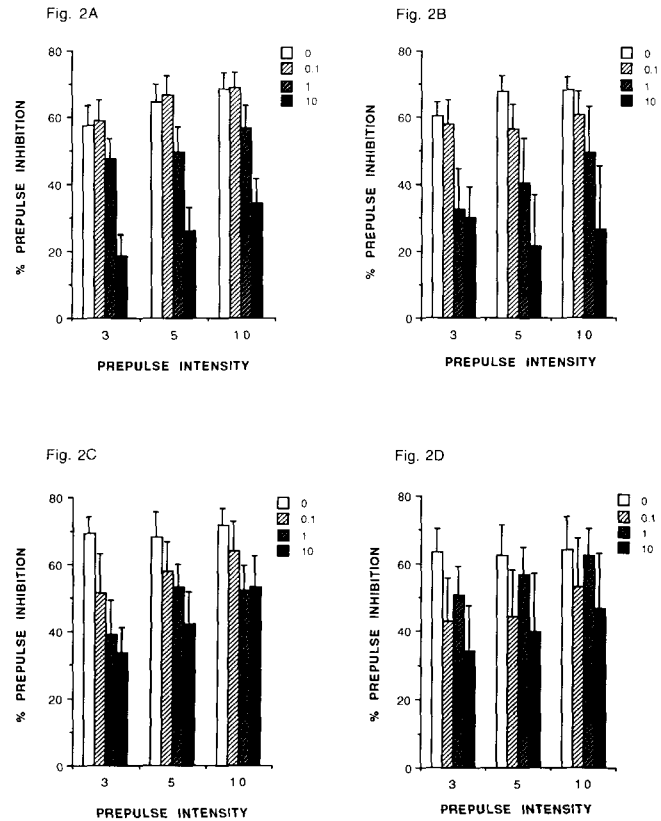

FIG. 2. Prepulse inhibition (PPI) after infusion of quinpirole (0, 0.1, 1, 10 μg) into four separate regions within the NAC: (A) lateral NAC, (B) central NAC, (C) medial NAC, (D) anteromedial NAC (coordinates in text). Quinpirole caused significant dose-dependent reduction of PPI in the lateral and central NAC ($p < 0.0005$ and $p = 0.04$, respectively), by individual ANOVA. The effect of quinpirole did not reach significance in the medial or anteromedial NAC.

previously (28), and was replicated in the two-injection study (below).

Histological inspection (Fig. 3) revealed injection sites distributed from the medial to the lateral extents of the nucleus accumbens. To further assess the relationship between injection location within the NAC and the PPI-disruptive effects of quinpirole, cannula placements were ranked in order of distance from the midline by an experimenter blind to the behavioral data (F.J.W.). A difference score was calculated by subtracting each rat's mean PPI value after 0.1, 1.0, or 10.0 μg of quinpirole from its own mean PPI value after 0 μg of quinpirole. A large difference score, thus, reflected a robust effect of quinpirole. Spearman rank correlation revealed that injector distance from the midline was positively correlated with the PPI-disruptive effect of quinpirole for the 10 μg dose ($R_s = 0.34, p = 0.05$). This correlation did not reach significance for the 0.1 or 1.0 μg doses of quinpirole ($p > 0.05$, both comparisons).

Because distance from the midline correlated significantly with the amount of quinpirole-induced PPI disruption only with the highest dose of quinpirole, it is possible that the lateral and medial accumbens have a different D_2 capacity for modulating PPI. Thus, although there is a comparable reduction in PPI after infusion of low doses of quinpirole into the lateral and medial accumbens, the PPI-disruptive effects of higher doses of quinpirole increase with increasingly lateral injection sites within the accumbens. Accordingly, the amount of additional loss of PPI in rats after the highest doses of quinpirole compared to the the lowest dose of quinpirole was significantly correlated with the distance from the midline (R_s

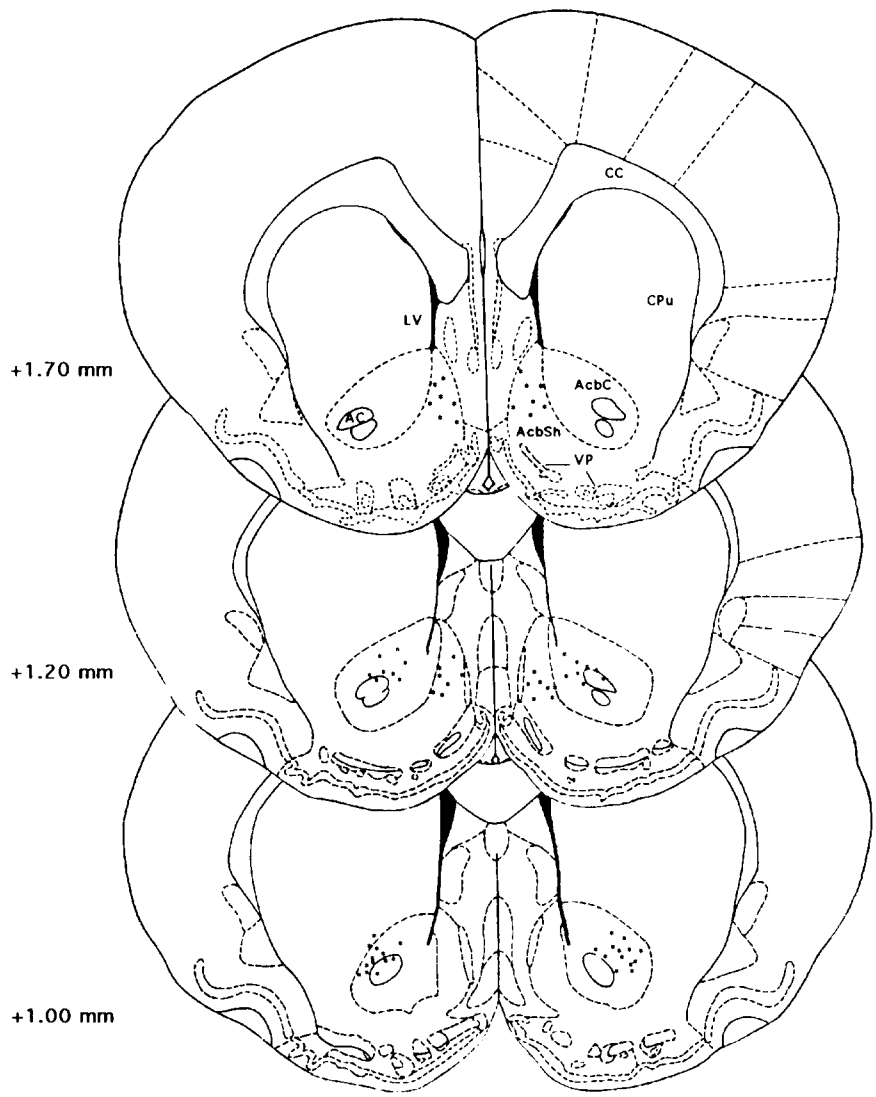

FIG. 3. Location of cannulae tips (*) in four separate subregions of the nucleus accumbens (NAC), plotted on modified sections from Paxinos and Watson (1986). Anterior-posterior level from bregma is indicated at left. Cannulae tracks were visible through the neocortex and striatum, and smaller needle marks penetrated ventral to the striatum into the NAC. AcbSh, nucleus accumbens shell; AcbC, nucleus accumbens core; AC, anterior commissure; CC, corpus callosum; CPu, caudate-putamen; VP, ventral pallidum; LV, lateral ventricle.

Fig. 4A

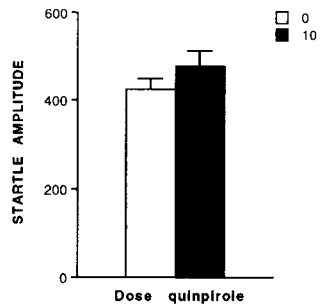

Fig. 4B

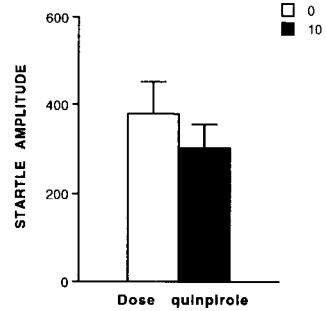

Fig. 4C

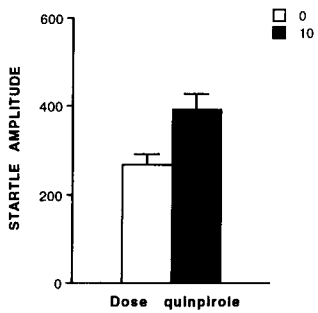

FIG. 4. Mean startle amplitude after infusion of either of 0 or 10 μg of quinpirole into three separate regions within the NAC: (A) lateral NAC, (B) medial NAC, (C) anteromedial NAC (coordinates in text). Quinpirole did not significantly affect startle amplitude, $F(1, 27) < 1$, NS).

Fig. 5A

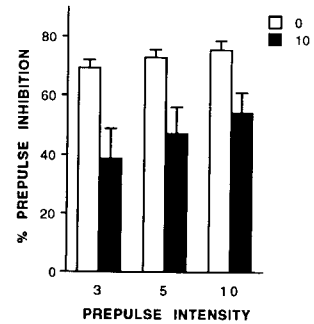

Fig. 5B

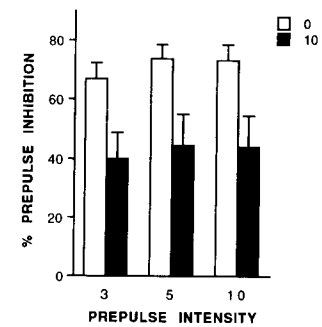

Fig. 5C

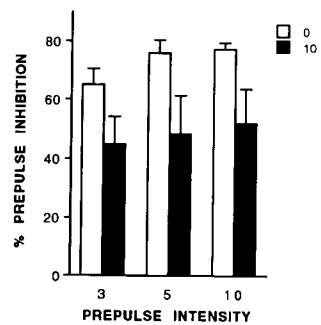

FIG. 5. PPI after infusion of either of 0 or 10 μg of quinpirole into three separate regions within the NAC: (A) lateral NAC, (B) medial NAC, (C) anteromedial NAC (coordinates in text). Independent ANOVAs with repeated measures on dose revealed a significant reduction in PPI after infusion into the lateral NAC ($p < 0.01$), the medial NAC ($p < 0.001$) or the anteromedial NAC ($p < 0.02$).

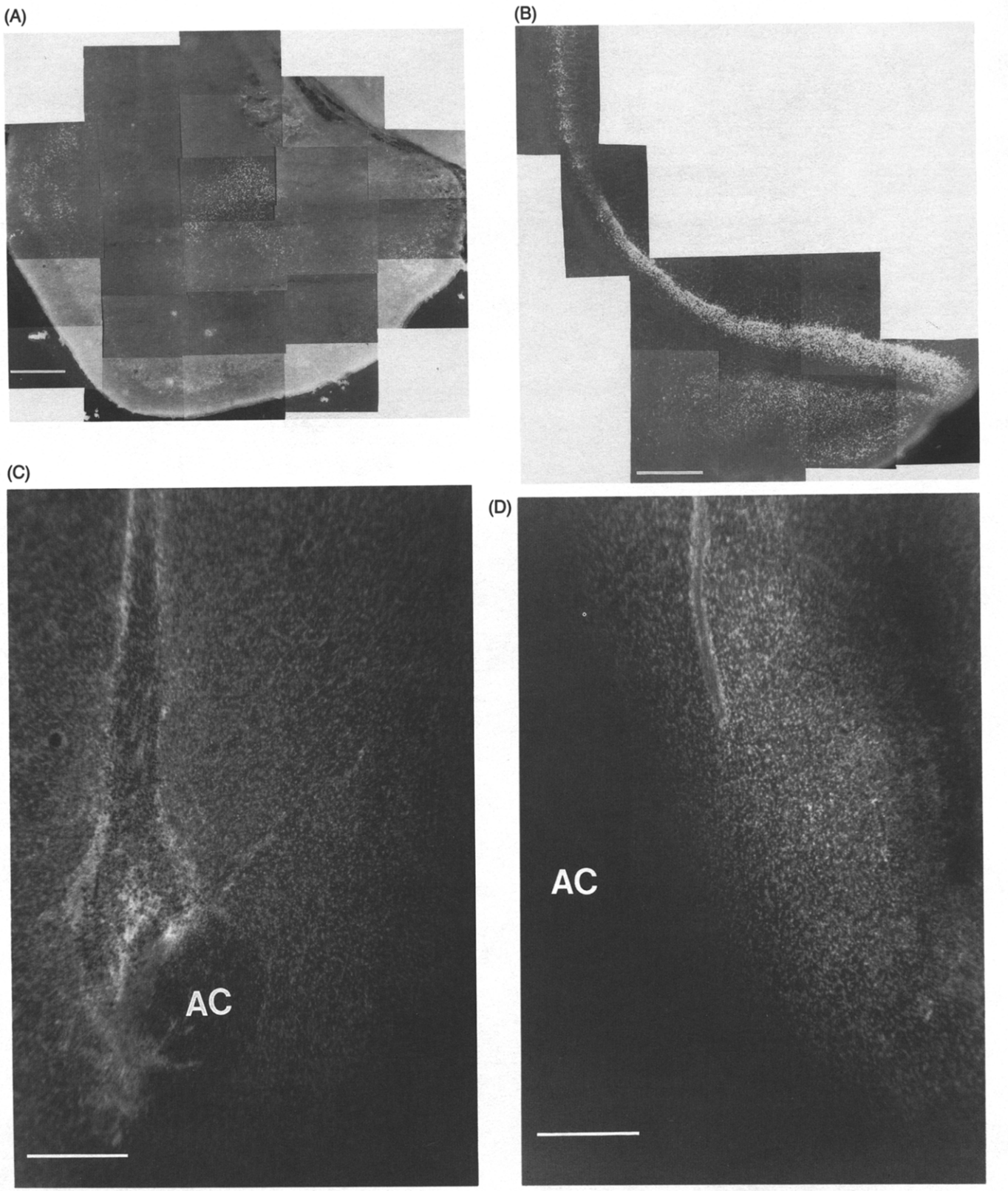

FIG. 6. Photomicrographs of fluorescent labeling in the left basolateral amygdala or ventral hippocampus following infusion of the retrograde tracer Nuclear yellow into the left lateral NAC and medial NAC. Basolateral amygdala (A) was mainly labeled after infusion into the lateral NAC. Ventral subiculum and CA1 field of the hippocampus (B) were labeled after NY infusion into the medial NAC, but not after NY infusion into the lateral NAC. Also shown are NY infusion sites in the lateral NAC (C) or medial NAC (D). AC, anterior commissure. Scale bars, 0.5 mm.

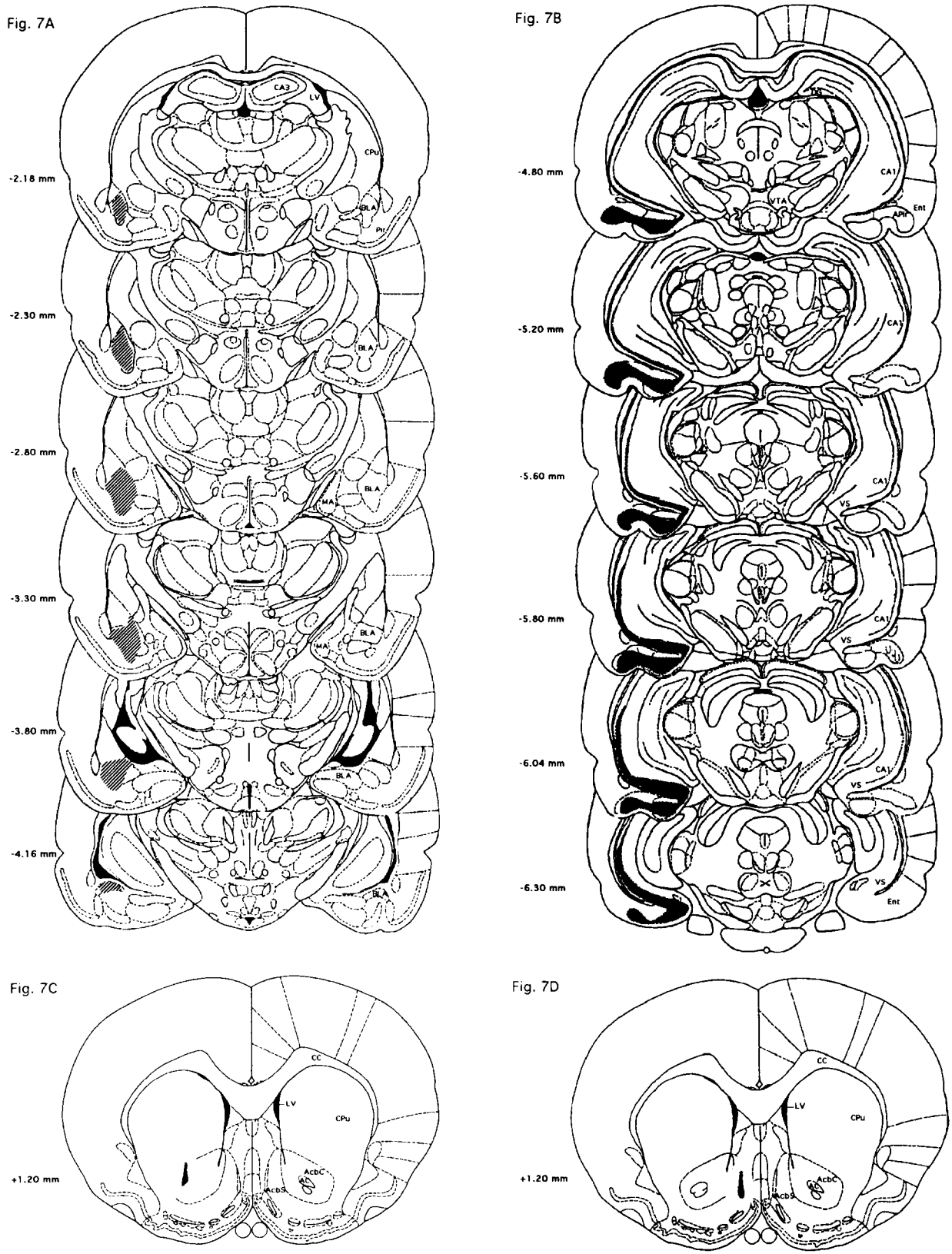

FIG. 7. Schematic representation of typical fluororescent labeling in the basolateral amygdala (A) and ventral hippocampus (B) after NY infusion into the lateral (C) and medial (D) NAC. Striped areas represent labeling in the basolateral amygdala; dotted areas represent labeling in the ventral hippocampus. The dotted areas in the (C) and (D) represent diffusion after NY infusion into the NAC. BLA, basolateral amygdala; VS, ventral subiculum; CA1, field CA1 of Ammon's horn; CA3, field CA3 of Ammon's horn; Ent, entorhinal cortex; Pir, piriform cortex; AcbS, accumbens shell; AcbC, accumbens core; AC, anterior commissure; CPu, caudate-putamen; LV, lateral ventricle; CC, corpus callosum.

= 0.36 p = 0.04). This increased D_2 capacity of lateral compared to medial regions of the accumbens is suggested by the fact that compared to the lowest dose of quinpirole (0.1 μg), PPI was significantly lower after injection of the highest dose of quinpirole (10.0 μg) in the lateral accumbens (F = 15.73) and central accumbens (F = 7.14), but not in the medial accumbens (F < 1) or anteromedial accumbens (F < 1).

Although the overall analyses of the four-injection study revealed no statistically significant effects of quinpirole infusion in medial and anteromedial accumbens regions in the above groups, examination of the data (Fig. 2) suggests that the highest dose (10 μg) of quinpirole infused into either of these regions did substantially reduce PPI. This observation is supported by data from the two-session study, in which a separate group of rats was studied after intra-NAC infusion of either 0 or 10 μg doses of quinpirole (Figs. 4–5). P-ALONE amplitude, analyzed using a two-way ANOVA with region as the between-subject factor and dose as the within-subject factor, revealed no significant effect of quinpirole (F < 1) (Fig. 4). PPI, analyzed using a two-way ANOVA with region as the between-subject factor and dose and prepulse type as within-subject factors, revealed a significant effect of dose, $F(1, 27)$ = 26.42, $p < 0.0001$, and a significant effect of prepulse type, $F(2, 54)$ = 9.81, $p < 0.001$. There was no significant effect of region, or significant interactions of dose × region or dose × region × prepulse type (F < 1, all comparisons). Independent ANOVAs with repeated measures on dose revealed a significant reduction in PPI after infusion into the lateral NAC, $F(2, 24)$ = 5.72, $p < 0.01$, the medial NAC, $F(1, 8)$ = 23.69, $p < 0.001$, or the anteromedial NAC, $F(1, 7)$ = 8.32, $p < 0.02$ (Fig. 5).

Infusions of Nuclear yellow (NY) into lateral or medial NAC resulted in retrograde labeling of neurons in the medial prefrontal, entorhinal, and piriform cortices (not shown). The amygdaloid complex and hippocampal formation were densely labeled as well. After NY infusions in the lateral accumbens (Figs. 6C and 7C), cells were labeled in the amygdaloid complex, primarily in the basolateral amygdala, and to a much lesser degree in the medial amygdala (Figs. 6A and 7A). After NY infusions in the medial accumbens (Figs. 6D and 7D), cells were labeled in the ventral subiculum and CA1 field of the hippocampus (Fig. 6B and 7B). Cells in subcortical structures, including the ventral tegmental area and the ventral pallidum, were labeled following infusion into either of two accumbens regions, although cells in the substantia nigra pars compacta were labeled after NY infusion into the lateral NAC.

DISCUSSION

The NAC has been described as a heterogeneous structure that can be divided into at least two major subregions, a lateral core region and a ventromedially located shell region. Recent anatomical studies offer compelling evidence that connectional, cytoarchitectual, and neurochemical properties distinguish core and shell regions (29). For example, axonal tracing studies indicate considerable specificity in the afferent and efferent organization of NAC core and shell regions. The lateral accumbens core region receives inputs primarily from prelimbic cortex, rostral basolateral amygdala, and dorsal subiculum of the hippocampus. Neurons within the core subregion send efferent projections to dorsolateral ventral pallidum and entopeduncular nucleus (11,12,29). The medial shell region of the NAC receives afferents from infralimbic or piriform cortices, caudal basolateral amygdala, and ventral subiculum of the hippocampus. Shell neurons then innervate posteromedial ventral pallidum, sublenticular substantia innominata, lateral hypothalamus, and mediodorsal thalamus (10,11). The NAC core and shell subregions also differ in their basal and stimulated levels of dopamine metabolism (7).

In the present study, we replicated our previous finding that NAC D_2 receptor stimulation reduces PPI in rats (24,28). The present results also suggest that the anatomical substrates of the accumbens D_2 modulation of sensorimotor gating may be characterized by a weak medial-to-lateral gradient, but certainly are not as clearly demarcated as are the regional differences in accumbens afferent connections. Thus, despite clear differences in limbic cortical inputs to medial and lateral accumbens injection sites, verified by the patterns of retrograde-labeled cells after NY injections, there was a significant reduction in PPI after quinpirole infusion into either medial or lateral accumbens. It appears that the accumbens D_2 substrates that modulate sensorimotor gating are distributed across the body of the NAC, crossing regions innervated by very distinct limbic cortical regions and, thus, do not form a clearly segregated functional subunit.

Although the primary startle circuit is mediated by brain circuity at or below the level of the lateral lemniscus (5), PPI is modulated by forebrain circuitry connecting portions of the limbic cortex (4), ventral striatum (22,28), ventral pallidum (21), and pontine reticular formation (25). The limbic cortical modulation of PPI is affected by portions of dorsal and ventral subiculum (4), and may also include other hippocampal and nonhippocampal regions. It has been proposed that accumbens D_2 substrates gate the efflux of limbic cortical information to subcortical structures involved in the initiation of goal-directed behaviors (15). The present results suggest that the D_2 modulation of sensorimotor gating is distributed across accumbens subregions that receive differential inputs from either the ventral hippocampus or the basolateral amygdala.

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