Pharmacology Biochemistry and Behavior, Vol. 61, No. 1, pp. 113–119, 1998

0091-3057/98 $19.00 + .00

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PII S0091-3057(98)00079-3

Localizing Haloperidol Effects on Sensorimotor Gating in a Predictive Model of Antipsychotic Potency

SHARRON HART, MARWAN ZREIK, RUTH CARPER AND N. R. SWERDLOW

Department of Psychiatry, UCSD School of Medicine, La Jolla, CA 92093-0804

Received 7 November 1997; Revised 9 February 1998; Accepted 27 February 1998

HART, S., M. ZREIK, R. CARPER AND N. R. SWERDLOW. *Localizing haloperidol effects on sensorimotor gating in a predictive model of antipsychotic potency*. PHARMACOL BIOCHEM BEHAV **61**(1) 113–119, 1998.—The degree to which a startle response to a loud noise is inhibited by a weak prestimulus is an operational measure of sensorimotor gating. Prepulse inhibition (PPI) can be measured across species and is reduced in schizophrenia patients and dopamine (DA)-activated rats. The ability of DA antagonists to restore PPI in apomorphine (APO)-treated rats correlates highly with their clinical antipsychotic potency. We compared the ability of systemic- vs. intracerebrally (IC)-administered haloperidol (HAL) to restore PPI in APO-treated rats. Consistent with previous studies, systemic administration of HAL completely restored PPI in rats treated with APO (0.5 mg/kg SC), with an ED_{50} of approximately 0.02 mg/kg. In an otherwise identical paradigm, HAL failed to fully restore PPI after infusion into either the nucleus accumbens (NAC_{core} or NAC_{shell}), NAC_{core} + caudate nucleus (CN), ventral subiculum (VS), medial prefrontal cortex (MPFC), or ventral tegmentum (VTA). A subtotal, but statistically significant restoration of PPI was achieved after HAL infusion into all regions, except the NAC_{shell}. Statistically significant effects of ic HAL tended to be observed at doses that were only approximately 5–10-fold lower than those at which significant effects were observed after systemic administration. The results suggest that systemically administered HAL may restore PPI in APO-treated rats through its action distributed throughout multiple levels of PPI-regulatory circuitry. © 1998 Elsevier Science Inc.

Antipsychotic Apomorphine Dopamine Haloperidol Prepulse Schizophrenia Sensorimotor Startle

SENSORIMOTOR gating is the involuntary or preattentive reduction of a motor response via inhibitory processes triggered by a sensory event. Prepulse inhibition (PPI) is an operational measure of sensorimotor gating in which the robust response to a startling stimulus (e.g., noise pulse) is inhibited when this pulse is preceded 30–500 ms earlier by a weak prepulse (8,10).

PPI can be studied across species and is significantly reduced in schizophrenia patients (1,2,9) and in dopamine (DA)-stimulated rats (5,16,23). The ability of antipsychotic compounds to restore PPI in apomorphine (APO)-treated rats strongly correlates with their clinical antipsychotic potency (20).

It is not known where in the brain antipsychotics act to restore PPI in APO-treated rats. Because of the putative linkage between this effect of antipsychotics and their clinical potency, it may be extremely valuable to identify such a location of antipsychotic action.

The present study investigated the PPI-disruptive effects of APO in rats after infusion of the D_2 antagonist haloperidol systemically, or into several brain regions that are implicated in the regulation of PPI, in an attempt to localize a critical "site of action" of haloperidol, i.e., where it acts to restore PPI in APO-treated rats. Compared to the ability of systemic-administered haloperidol to restore PPI in APO-treated rats, it was predicted that significantly lower doses of haloperidol would restore PPI after infusion into such a "site of action."

Several specific brain regions might be likely candidates for such a "site of action" for the antipsychotic restoration of PPI in APO-treated rats. The nucleus accumbens (NAC) is a known substrate for the dopaminergic regulation of PPI.

Requests for reprints should be addressed to N. R. Swerdlow, Department of Psychiatry, UCSD School of Medicine, La Jolla, CA 92093-0804.

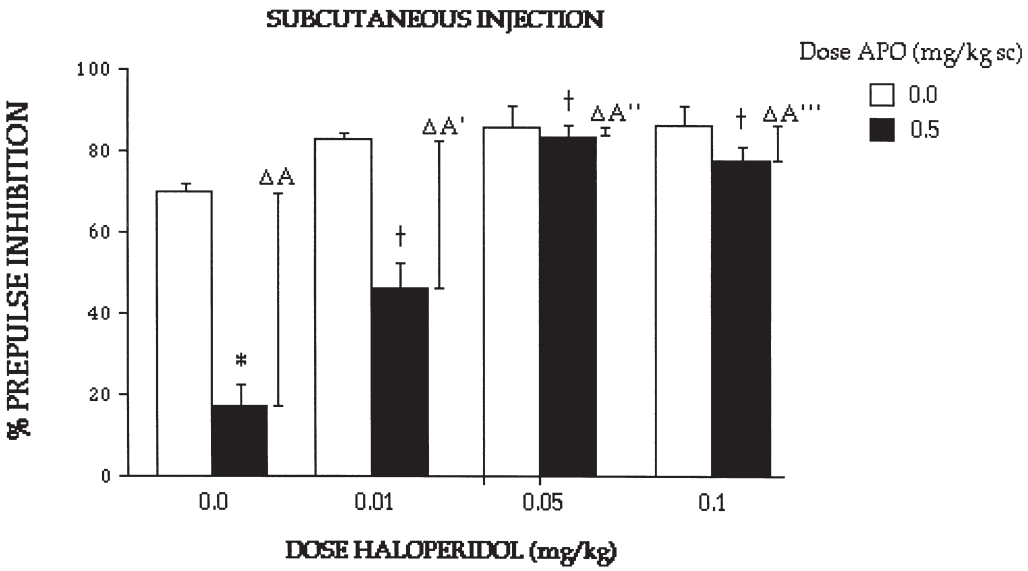


FIG. 1. Effects of systemically administered haloperidol on the PPI-disruptive effects of APO. Statistical analyses are reported in Table 1. The magnitude of the "impact" of APO on PPI is indicated by A, A′, A′′ and A′′′ for rats pretreated with vehicle, 0.01, 0.05, or 0.1 mg/kg HAL, respectively. *Significant main effect of APO, $p < 0.0001$; (†significantly greater than haloperidol vehicle, $p < 0.05$, by Tukey comparison after significant main effect of HAL in APO-treated rats by one-factor ANOVA. All error bars represent SEM.

Dopamine (DA) or DA agonist infusion into this area reduces PPI (19,20,27), while NAC DA depletion prevents the PPI-disruptive effects of the indirect DA agonist amphetamine (25) and enhances the PPI-disruptive effects of APO (23); the latter effect is thought to reflect DA receptor denervation supersensitivity. Other manipulations of the NAC, such as electrolytic (14) or excitotoxic lesions (13) and infusion of non-NMDA glutamate agonists (28) or compounds with activity on adenosine or glycine substrates (15), also significantly modify PPI.

The caudate nucleus (CN) is also implicated in the DAergic regulation of PPI. PPI is reduced by DA infusion into the anteromedial striatum (21). Additionally, lesions of the dorsal posterior caudate significantly reduce PPI (12).

Pharmacological or surgical manipulations of the ventral subiculum (VS) are known to modify PPI. PPI is significantly reduced by NMDA infusions into the VS (26), or by infusions of the cholinergic agonist carbachol into the VS (4). Additionally, VS lesions significantly enhance the PPI-disruptive effects of APO (24).

The ventral tegmentum (VTA) might be considered another candidate "site of action" of antipsychotics in this measure. The VTA is the source of DA cells within the PPI-regulating mesolimbic DA system (18). Although antipsychotic properties are most associated with the impact of these drugs on postsynaptic DA receptors in forebrain terminal fields, the potent effects of antipsychotics on cellular activity in the VTA are also well documented (3). Certain manipulations of the VTA, such as infusion of pertussis toxin, also significantly modify PPI (29).

The last candidate region to be examined in these studies is the medial prefrontal cortex (MPFC). 6-Hydroxydopamine lesions to the MPFC reduce PPI, and this effect is reversed by systemic treatment with HAL (11). Also, cell lesions of the MPFC significantly enhance the PPI-disruptive effects of APO (24). Thus, there is experimental evidence to suggest the possible involvment of the nucleus accumbens, caudate nucleus, hippocampus, ventral tegmental area, or medial prefrontal cortex in the ability of antipsychotics to restore PPI in APO-treated rats. We compared the ability of HAL to restore

TABLE 1

STATISTICAL ANALYSES OF DRUG EFFECTS ON PPI

HAL Injection Site	Effect of HAL in APO-Treated Rats
Subcutaneous	$F(3, 26) = 44.11, p < 0.0001$
NAC_{core}	$F(3, 28) = 3.44, p < 0.035$
NAC_{shell}	$F(3, 31) = 2.09$, NS
NAC_{core} + CN	$F(3, 22) = 6.20, p < 0.005$
MPFC	$F(3, 27) = 8.09, p < 0.0005$
VS	$F(3, 27) = 6.93, p < 0.002$
VTA	$F(3, 24) = 5.70, p < 0.005$

TABLE 2

ED_{50} FOR HALOPERIDOL RESTORATION OF PPI IN APO-TREATED RATS*

HAL Injection Site	ED_{50} (μg Total Dose)
Subcutaneous	9.24
VS	7.10
MPFC	8.29
NAC_{core}	5.61
NAC_{core} + CN	1.84

* Dose interpolated to reduce APO-induced reduction of PPI by 50% (see the Method section).

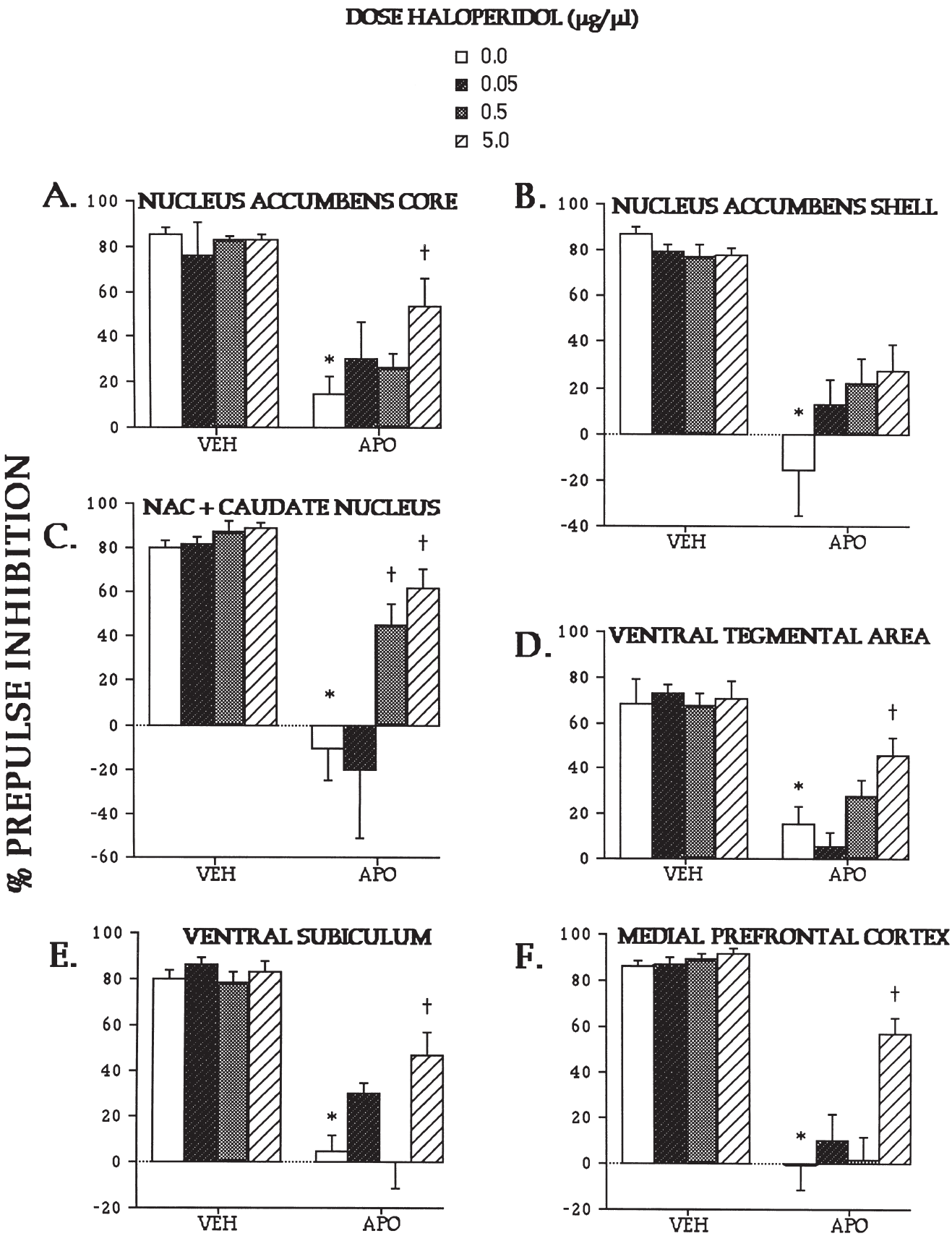


FIG. 2. Effects of intracerebrally administered haloperidol on the PPI-disruptive effects of APO. Statistical analyses are reported in text and Table 1. *Significant main effect of APO, $p < 0.0001$; †significantly greater than haloperidol vehicle, $p < 0.05$, by Tukey comparison after significant main effect of HAL in APO-treated rats by one-factor ANOVA. All error bars represent SEM.

TABLE 3
STATISTICAL ANALYSES OF DRUG EFFECTS ON PULSE-ALONE MAGNITUDE

HAL Injection Site	Main Effect of APO	Main Effect of HAL	APO × HAL Interaction
Subcutaneous	$F < 1$	$F(3, 26) = 2.14$, NS	$F < 1$
NAC_{core}	$F < 1$	$F < 1$	$F < 1$
NAC_{shell}	$F(1, 31) = 1.34$, NS	$F < 1$	$F < 1$
NAC + CN	$F < 1$	$F < 1$	$F < 1$
MPFC	$F < 1$	$F < 1$	$F < 1$
VS	$F < 1$	$F < 1$	$F < 1$
VTA	$F < 1$	$F < 1$	$F(3, 24) = 2.39$, NS

PPI in APO-treated rats after systemic administration of HAL vs. intracerebral infusion of HAL into these brain regions.

METHOD

Two-hundred and thirteen male Sprague–Dawley rats (225–250 g) were housed in groups of two or three and maintained on a reversed 12 h:12 h schedule (lights off at 0700 h). Food and water were provided ad lib. All behavioral testing was performed during the dark phase (6). Rats were handled individually within 3 days of arrival, and had cannulae surgically implanted beginning 7 days after arrival.

To localize the site of action of haloperidol (HAL) in restoring PPI in apomorphine (APO)-treated rats, bilateral injections were made into seven brain areas or combination of areas. Equithesin-anesthetized rats were shaved and placed in a Kopf stereotaxic holder, with blunt ear bars that do not puncture the tympanic membranes. Stainless steel 23-ga guide cannulae were implanted bilaterally using dental cement and screws, to a depth 3 mm above the target injection site. Cannulae were filled with wire stylets, wounds were closed with surgical clips, and animals were observed until fully recovered. Coordinates for the injections were as follows: NAC_{core}, AP +3.2, L ±1.7, DV −7.8 from skull, +5.0 toothbar; NAC_{shell}, AP +1.2, L ±0.8, DV −7.3 from skull, −3.3 toothbar; CN, AP +0.4, L ±3.3, DV −4.7 from skull, +5.0 toothbar; VTA, AP −2.8, L ±0.5, DV −8.8 from skull, +5.0 toothbar; MPFC, AP +3.2, L ±0.7, DV −4.2 from skull, −3.3 toothbar; VS, AP −6.5, L ±5.0, DV −8.0 from skull, −3.3 toothbar.

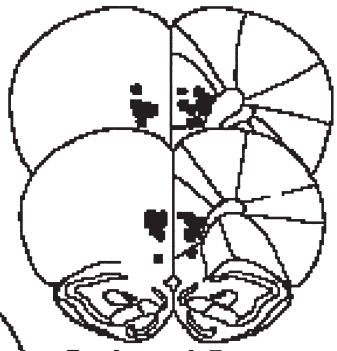
The effects of HAL injected bilaterally into specific brain areas on APO-disrupted PPI were studied during two test sessions, 7 days apart. Rats were assigned to one of four HAL dose groups (vehicle, 0.05, 0.5, or 5.0 μg/side) matched for startle amplitude during a baseline testing session administered 7–9 days after surgery. HAL was dissolved in water and 3% lactic acid. APO was dissolved in saline with 0.1% ascorbic acid. HAL dose was kept constant for each rat across both test days; dose APO (vehicle vs. 0.5 mg/kg SC) was alternated, with dose order balanced across test days. In this manner, dose HAL was the between-subject variable, and dose APO was the within-subject variable. This dose of APO has been repeatly demonstrated to maximally disrupt PPI (23); the doses of HAL used in systemic treatments (0.01, 0.05, and 0.1 mg/kg SC) have been repeatedly demonstrated to restore PPI in APO-treated rats (22).

Each of four startle chambers (SR-LAB, San Diego Instruments, San Diego, CA) 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 that also digitized (0–4095), rectified, and recorded stabilimeter readings, with 100 samples collected at 1-ms intervals 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 Super-tweeter (frequency response predominantly between 5–16 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). Chambers were also balanced across all experimental 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.

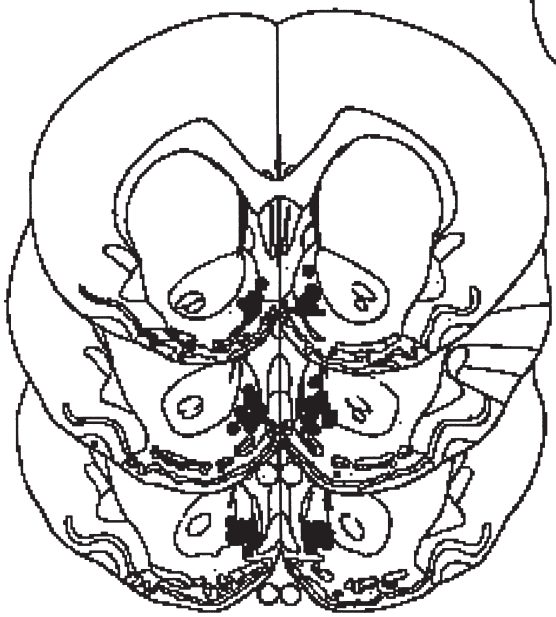
For studies using bilateral intracerebral infusion of HAL, each rat was pretreated with one dose of HAL (vehicle, 0.05, 0.5, or 5.0 μg in 1.0 μl/side). Briefly, wire stylets were removed, and replaced bilaterally with a 30-ga stainless steel needle attached to a Hamilton syringe and motor pump via PE tubing. Infusion rate was 1 μl/170 s. Needles were left in place for 60 s postinfusion, then removed and replaced with a wire stylet. Rats were treated 10 min later with APO (vehicle or 0.5 mg/kg SC) and immediately placed in the startle chambers for a 5-min acclimation period with 70 dB(A) background noise.

After the acclimation period, rats were tested in a session that included three types of stimuli: PULSE (120 dB(A) 40-ms broad band burst), PREPULSE (85 dB(A) 20-ms broad band burst presented 100-ms prior to PULSE), or NOSTIM. The session was structured into three blocks of 21 trials to allow assessment of the effects of drug over time, which might provide information related to the impact of drug diffusion. Trials were presented in pseudorandom order, with a variable intertrial interval (average 15-s).

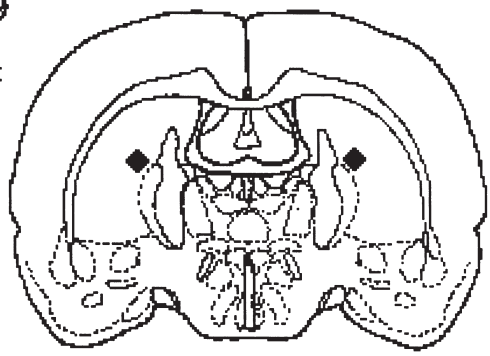
FIG. 3. Representative locations of IC injection sites for data reported in Fig. 2. In most cases, formalin-fixed brain tissue was cut in 100 μm coronal sections, and the ventral extent of each injector path was marked with a solid dot (•) on a figure modified from (17). Because many injection sites were densely packed within some target regions, larger solid markings represent regions containing dense groupings of injector tips.



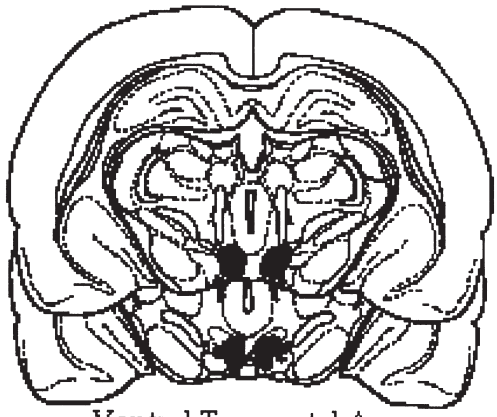
Prefrontal Cortex



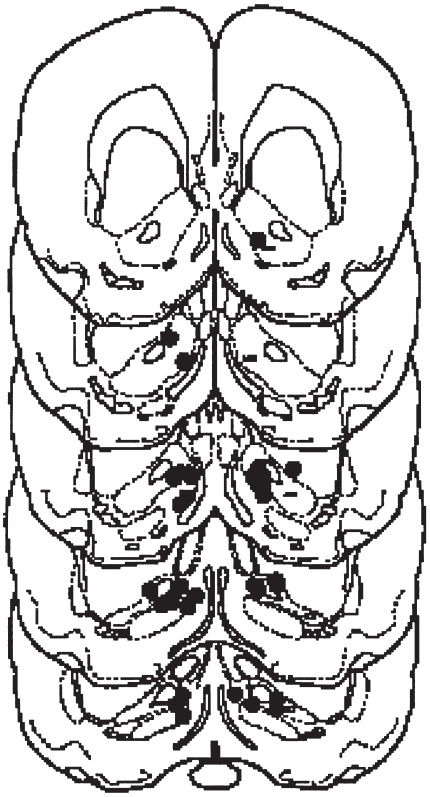
Nucleus Accumbens Shell



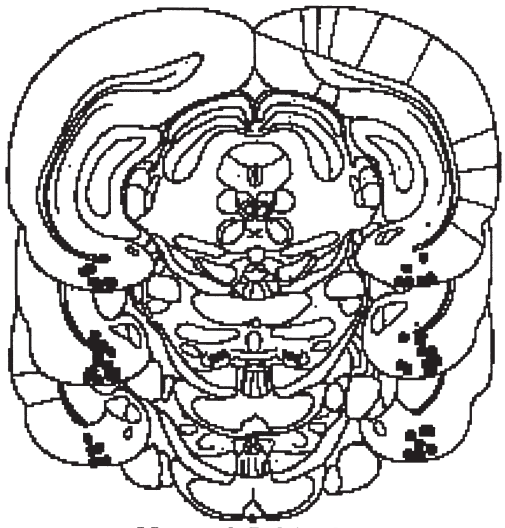
Caudate Nucleus



Ventral Tegmental Area



Nucleus Accumbens Core



Ventral Subiculum

On completion of behavioral testing, most rats were sacrificed by sedative overdose and perfused transcardially with 10% formalin/saline. Brains were removed, and cannula tips were located using 100-μm tissue sections. Rats with errant cannula locations were excluded from analysis.

Startle data were analyzed by mixed-design analyses of variance (ANOVAs). PPI was defined as the percent reduction in startle amplitude in the presence of the prepulse compared to the amplitude in the absence of the prepulse ($100 \times [(A-AP)/A]$, where "A" is the amplitude on PULSE trial and "AP" is the amplitude on prepulse trial. Repeated measure ANOVAs, with APO dose as the within-subject factor, and HAL dose as the between-subject factor, were completed for each individual brain region. To compare across brain regions, a two-factor ANOVA was completed, using % PPI in APO-treated rats as the dependent variable, and HAL dose and brain regions as the two grouping factors. A significant HAL × brain region interaction on PPI prompted post hoc assessments of individual doses via one-factor ANOVAs; alpha was set at 0.05.

Relative potencies of HAL were compared across the various injection sites using an operational ED_{50}. Briefly, an overall magnitude of an APO effect was calculated for each site as (%PPI APO vehicle minus %PPI APO 0.5 mg/kg, or "ΔA" in Fig. 1). This value represents the "impact" of APO on PPI in any particular group of rats, i.e., the amount by which APO reduces PPI. The ability of a dose of HAL to restore PPI was calculated as: 1 minus ("impact" of APO after HAL dose X)/("impact" of APO after HAL vehicle)]. In Fig. 1, these values were calculated as $[1 - (\Delta A'/\Delta A)]$, $[1 - (\Delta A''/\Delta A)]$ and $[1 - (\Delta A'''/\Delta A)]$, for 0.01, 0.05, and 0.1 mg/kg HAL doses, respectively. Thus, a calculated value of 0.5 indicated a dose of HAL that reduced the "impact" of APO by 50%, and was used as an operational ED_{50}, for comparison across injection sites.

RESULTS

Systemic HAL administration significantly restored PPI in APO-treated rats at doses between 0.01 and 0.1 mg/kg. In rats treated with HAL vehicle, APO reduced PPI by 52.63%, from 69.87% inhibition to 17.24% inhibition (Fig. 1). This "impact" of APO (A) was reduced to 36.66% in rats pretreated with 0.01 mg/kg HAL (A′) and to 2.44% in rats pretreated with 0.05 mg/kg HAL (A′). The operational ED_{50} for systemic HAL injection (based on an assumption of linear dose effects in this 0.01–0.05 mg/kg range) was interpolated to be 0.028 mg/kg (approximately 9.24 μg total dose HAL) (Fig. 1; Tables 1 and 2). Calculated in this same manner, ED_{50}'s for the NAC_{core}, NAC_{core}+CN, MPFC, and VS were 5.61, 1.84, 7.1, and 8.29 μg total dose HAL, respectively (Table 2). No doses of HAL in this study reduced the "impact" of APO on PPI by 50% or more, after HAL infusion into the VTA or NAC_{shell}.

Individual repeated measure ANOVAs were performed for each brain region, with APO dose as a within-subject factor and HAL dose as a between-subject factor (Table 1). To enhance the sensitivity to detect possible interregional differences in the sensitivity to HAL, an overall two-factor ANOVA was performed, using percent PPI in APO-treated rats as the dependent variable and brain region and HAL dose as the grouping factors. This analysis revealed a significant main effect of HAL, $F(3, 158) = 18.98$, $p < 0.0001$, no significant effect of brain region, $F(5, 158) = 1.41$, NS, and a significant HAL × region interaction, $F(15, 158) = 1.85$, $p < 0.035$. To pursue the significant HAL × region interaction, one-way ANOVAs were performed for each region, comparing percent PPI in APO-treated rats under HAL vehicle vs. HAL active dose conditions (Table 1). HAL significantly restored PPI in APO-treated rats after infusion into all of the regions tested except the NAC_{shell}. The lowest dose of HAL to significantly reverse the PPI-disruptive effects of APO was 5.0 μg per side (10 μg total dose HAL) for the NAC_{core}, VTA, VS, and MPFC; simultaneous bilateral infusion of HAL into the NAC_{core} and the caudate nucleus significantly restored PPI in APO-treated rats after infusion of 0.5 μg per side (2.0 μg total dose HAL) (Fig. 2).

The effects of APO and HAL on pulse-alone startle magnitude are seen in Table 3. Neither haloperidol nor APO had statistically significant effects on pulses alone startle magnitude, and no significant interactions were noted. Locations of IC infusion sites are represented in Fig. 3.

DISCUSSION

Haloperidol infusion into several different brain regions restored PPI in apomorphine-treated rats. Sensitivities to HAL observed across several of these infusion sites were comparable, with less than an order of magnitude separating the calculated ED_{50} for the ability of haloperidol to restore PPI in APO-treated rats, after infusion into the NAC_{core}, NAC_{core}+CN, MPFC or VS, or after systemic injection. Only the ED_{50}s for the NAC_{core}+CN (1.84 μg HAL) and NAC_{core} (5.61 μg HAL) were convincingly separated from that for systemic injection (9.24 μg HAL). One might view these data to suggest, as we have previously suggested based on the PPI-disruptive effects of regionally infused dopamine, that the DAergic regulation of PPI extends, at least, beyond the NAC proper, and into portions of the anteroventral caudate nucleus (13). The fact that systemic administration of HAL results in a physiological effect (restoration of PPI) with a potency comparable to that observed after localized intracerebral HAL administration further supports the notion that the substrates responsible for this effect of HAL on PPI are widely distributed throughout forebrain DA systems.

For all IC infusion locations, except the NAC_{shell}, 5.0 μg of intracerebral HAL per side (10 μg total HAL) significantly restored PPI in apomorphine-treated rats. This dose of haloperidol is also within an order of magnitude of the systemically administered dose of haloperidol that was required to significantly restore PPI in apomorphine-treated rats (0.01 mg/kg sc yields approximately 3.34 μg total HAL). A significant reversal of the apomorphine effect was observed after simultaneous infusion of a 10-fold lower dose of HAL into the NAC_{core}+CN.

The relative lack of effectiveness of intra-NAC_{shell} HAL in this measure is of interest, based on reports that PPI is differentially regulated by dopamine-glutamate interactions within the NAC_{core} and NAC_{shell}. Thus, HAL restores PPI after infusion of AMPA into the NAC_{core}, but not after AMPA infusion in the NAC_{shell} (28). The present results further suggest that NAC_{shell} substrates regulating PPI may be relatively less sensitivity to the PPI-restorative effects of DA receptor blockade, compared to the NAC_{core}.

More generally, these findings suggest that the action of systemically administered HAL in restoring PPI in apomorphine-treated rats cannot be clearly localized to a single brain region. Indeed, the nervous system regulation of PPI extends to numerous brain regions, and even portions of the peripheral nervous system have been implicated in the regulation of sensorimotor gating (7). It is conceivable that the present findings reflect the diffusion of HAL to a critical "site of ac-

tion" that was not included among those examined in these studies. This possibility of "diffusion artifact" is somewhat at odds with the observation that the effects of APO were significantly reversed after HAL infusion into the NAC_{core}, but not after HAL infusion into the closely neighboring NAC_{shell}. Alternatively, it is possible that HAL acts at several different brain sites simultaneously—at least within distributed accumbens and striatal regions—to reverse the PPI-disruptive effects of apomorphine.

Clinical antipsychotic potency is strongly predicted by drug effects in this measure. A finding that a distributed brain system regulates these haloperidol effects raises the possibility that antipsychotic compounds, such as haloperidol, may exert their therapeutic effects via simultaneous actions within multiple brain regions.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the excellent assistance of Mr. Navid Taaid, Mrs. Pamela Auerbach, and Mr. Chad Pratt for their contributions to data acquisition. N.R.S. is supported by MH 48381, MH 42228, MH 01436, MH 52885 and MH 53484.

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