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Haloperidol Blocks Increased Locomotor Activity Elicited by Carbachol Infusion Into the Ventral Hippocampal Formation

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BRENNER, D. M. AND M. E. BARDGETT. *Haloperidol blocks increased locomotor activity elicited by carbachol infusion into ventral hippocampal formation.* PHARMACOL BIOCHEM BEHAV **60**(3) 759–764, 1998.—Previous studies have demonstrated that stimulation of the ventral hippocampal (VH) formation (including the ventral CA1 and subicular areas) elicits increased locomotor activity in rats. The locomotor-activating effects of VH stimulation have been hypothesized to be mediated via hippocampal output to cortical and subcortical dopamine (DA) systems. This study examined whether increased locomotor activity produced by VH stimulation was blocked by pretreatment with a DA receptor antagonist, and whether DA metabolism in subdivisions of the nucleus accumbens, caudate-putamen, and prefrontal cortex was elevated by VH stimulation. Stimulation of the VH (defined as the ventral CA1 and its borders, ventral subiculum, and entorhinal cortex) with the cholinergic agonist carbachol was found to elevate locomotor activity, while pretreatment with the D_2 receptor antagonist haloperidol blocked this effect. Stimulation of the VH did not alter DA metabolism (i.e., ratio of the DA metabolites DOPAC or HVA/DA) in any of the brain regions studied. These results indicate that the increased locomotor activity elicited by VH stimulation is not associated with dramatic increases in DA metabolism, but that it does require tonic activation of D_2 receptors. © 1998 Elsevier Science Inc.

Hippocampus Dopamine Antipsychotic Nucleus accumbens Caudate-putamen Prefrontal cortex Rat

ALTERATIONS in hippocampal activity appear to influence the expression of locomotor activity in animals. Elevations in locomotor activity can be evoked by electrical or chemical stimulation of either the dorsal or ventral hippocampal (VH) formation (1,10,19,31,33) without producing overt seizure activity. The effects of hippocampal stimulation on locomotor activity may be mediated by forebrain and cortical motor systems. Hippocampal neurons send glutamatergic afferents to the nucleus accumbens (NA), prefrontal cortex, and medial caudate-putamen (12,13,17,24,32). Infusion of glutamate receptor antagonists into the NA blocks the increased locomotor activity produced by intrahippocampal infusion of carbachol, a cholinergic agonist (19). This finding demonstrates that the activation of glutamate receptors in the NA is required for the increased locomotor activity elicited by hippocampal stimulation.

Many neurons in the NA also express dopamine (DA) receptors, and several studies have suggested that DA may play an integral role in the increased locomotor activity induced by hippocampal stimulation. Intraaccumbens infusion of a D_2 receptor agonist has been shown to suppress the effects of VH stimulation on locomotor activity (33). However, destruction of midbrain DA neurons also reduces the increased locomotor activity produced by VH stimulation (31), suggesting that DA may indeed be required for hyperactivity elicited by hippocampal activation. It is possible that hippocampal stimulation increases locomotor activity by elevating DA release or metabolism in afferent brain regions, because Strecker and Moneta (27) found that excessive electrical stimulation of the hippocampus increases extracellular DA in the NA. In light of this data, elevated locomotor activity elicited by hippocampal stimulation may be sensitive to blockade by haloperidol, a D_2 receptor antagonist that suppresses increases in locomotor activity produced by DA-elevating drugs, such as amphetamine (3).

The present study was designed to determine if systemic pretreatment with haloperidol blocks the elevating effects of hippocampal stimulation on locomotor activity, and if hippocampal stimulation evokes an increase in DA metabolism in the forebrain and prefrontal cortex. In the first experiment,

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haloperidol or vehicle was injected intraperitoneally (IP) 5 min prior to hippocampal stimulation. Hippocampal stimulation was achieved by microinfusing the cholinergic agonist, carbachol, into the right and left VH formation (defined as the ventral CA1 and its borders, ventral subiculum, and entorhinal cortex). Locomotor activity (number of photobeam breaks) was recorded in 5-min bins for 30 min before and after stimulation. In the second experiment, rats were killed 30 min after carbachol or vehicle infusion, and the nucleus accumbens shell and core, the medial and laterodorsal caudate-putamen, and the infralimbic and prelimbic cortices were microdissected. Levels of DA, 3,4-dihydrophenylacetic acid (DOPAC), and homovanillic acid (HVA) were determined in tissue samples by high-performance liquid chromatography, and two measures of DA metabolism, the ratio of DOPAC/DA and of HVA/DA (9), were compared between stimulated and unstimulated animals.

METHOD

Animals

Adult male Sprague–Dawley rats (Harlan, Indianapolis, IN) weighing approximately 350 g were used in all of the experiments. The rats were housed three per cage and given food and water ad lib. Lighting was kept on a 12/12 h light/dark schedule with the lights on at 2030 h. Each rat was handled for 5 min on each of the 3 days prior to experimentation to reduce the effects of handling stress in the experiments. Rats were handled every day following surgery until the experiments were completed. Experimental procedures were performed according to the current Guide for the Care and Use of Laboratory Animals (USPHS) under a protocol approved by the Washington University Animal Studies Committee.

Cannulation

One week prior to experimentation, rats were anesthetized with a ketamine/xylazine (30/1 mg/kg, IP respectively) solution and placed into a Kopf stereotaxic apparatus. The skull was exposed via incision and four stainless steel screws were inserted into the skull. Bilateral holes were then drilled into the skull over the CA1/subicular region of the VH. Two 23-gauge, 18-mm stainless steel cannulae (Small Parts, Miami Lakes, FL) with protective 30-gauge stainless steel guide wires were implanted into the VH with coordinates proportional to their spatial relationship to bregma [AP −6.0 mm, ML ±5.2 mm, V −7.7 mm, based on (21)]. Each guide cannula was fixed to the skull with dental acrylic (TMJ Instrument Co. Norco, CA).

EXPERIMENT 1: EFFECTS OF HALOPERIDOL ON INCREASED LOCOMOTOR ACTIVITY INDUCED BY INTRAHIPPOCAMPAL CARBACHOL

Habituation

One day prior to testing, rats ($n = 15$) were acclimated to behavioral testing cages equipped with two infrared photoelectric beams as previously described (4). The clear Plexiglas testing cages were 51 cm long × 26.5 cm wide × 32 cm high. Two photoelectric sensors projected beams of visible red light across the width of the testing cage at 17 and 34 cm along the length of the cage and at a height of 7 cm from the bottom of the cage. The photoelectric sensors were connected to counters that tabulated the number of breaks in the photobeam. Thirty minutes after being placed in the cages, each rat's guide wire was removed, and 30-gauge, 20-mm stainless steel needles were inserted into the right and left cannulae. After 2 min, the guide wires were placed back into the cannulae, and each rat was returned to the testing cage for another 30 min. The acclimation and testing procedures were performed in a darkened room and lasted approximately 1 h.

Testing

On experimentation days, rats were placed in the testing cages and the number of photobeam breaks were culminated every 5 min. Twenty-five minutes after the beginning of testing, each rat received a IP injection of either 0.1 mg/kg of haloperidol (Sigma) or saline, and was then returned to the test cage. The dose of haloperidol was based on a previous study by Kalivas et al. (16), which demonstrated that this dose of haloperidol effectively reduced increases in locomotor activity elicited by chemical stimulation of the ventral tegmental area. Five minutes later, each rat was removed from its testing cage and infused with 0.2 μl of a 2-mg/ml solution of either carbachol (Sigma, St. Louis, MO) or artificial cerebrospinal fluid (ACSF) containing 2.7 mM KCl, 145 mM NaCl, 1.0 mM $MgCl_2$, 1.2 mM $CaCl_2$, 2.0 mM Na_2HPO_4, pH 7.4. All chemicals used in the ACSF were obtained from Sigma. The dose of carbachol was based on earlier work by Mogenson and Nielsen (19) and Flicker and Geyer (10), which demonstrated its effectiveness in increasing locomotor activity after intrahippocampal infusion. Both solutions were infused through the chronic guide cannulae with 30-gauge, 20-mm stainless steel injection needles connected by PE-10 polyethylene tubing to Hamilton microsyringes. All infusions were made over 1 min, and were controlled by a Harvard infusion pump. Needles remained in place for one extra minute to avoid infusion media back flow. Photobeam breaks were then culminated for each 5-min period over a 30-min postinfusion interval. Each animal was tested in a counterbalanced order under each of four experimental conditions: saline + ACSF, saline + carbachol, haloperidol + ACSF, haloperidol + carbachol. Testing was performed every 3 days. After the final experiment, all animals were killed by chloral hydrate (850 mg/kg) overdose, received intracardiac perfusions of 4% paraformaldehyde for 20 min, and brains were stored in 30% sucrose/0.1 M KPBS until histological verification of cannulae placement was performed (see below).

EXPERIMENT 2: EFFECT OF INTRAHIPPOCAMPAL CARBACHOL ON DA TURNOVER IN AFFERENT BRAIN REGIONS

The same infusion protocol was followed as in the behavioral experiment described above. In this experiment, animals were tested only once ($n = 24$, $n = 12$ per group). Thirty minutes after bilateral infusion of carbachol or ACSF, animals were immediately decapitated.

Microdissection

The microdissection protocol was identical to that described by Bardgett et al. (5). The brain from each rat was rapidly removed and placed in a cold brain matrix (RBM 4000C, Activational Systems Inc., Warren, MI). The brains were then positioned between razor blades placed 4 mm from the anterior end of the matrix and 5 mm from the posterior end. With the brain in place, 1 mm coronal brain slices containing all of the relevant brain areas were obtained by placing razor blades at 5 and 6 mm (the NA core and shell, medialm and laterodorsal caudate-putamen) and at 3 and 4 mm (infralimbic and prelimbic portions of the prefrontal cortex) posterior to the

anterior razor blade (see Fig. 1). These slices were carefully removed from the matrix, and while adhering to the posterior razor blade, placed on a block of dry ice for 30 s. The right and left NA core areas were then punch dissected with a 840-μm diameter piece of cold stainless steel tubing that contained a stylet for punch removal. The anterior commissure was included in the dorsolateral aspect of the punch (Fig. 1). The right and left NA shell areas were then dissected with a 1600-μm diameter cold stainless steel tube with the void left by the NA core punch included in the dorsolateral aspect of the shell punch (Fig. 1). The right and left medial caudate-putamen were dissected with the 840-μm diameter tube that was placed directly dorsal to the shell punch. The left and right laterodorsal caudate-putamen were dissected with the 840-mm diameter tube that was placed in the extreme laterodorsal aspect of the striatum. The prefrontal cortex was dissected utilizing the 1600-μm diameter tube placed over the infralimbic and the prelimbic portions of this region (Fig. 1). Immediately after removal, the punches from the left and right sides of each brain region were combined in 1.5-ml polypropylene tubes, placed on dry ice, and stored at −80°C until the time of assay. The remaining posterior portion of the brain was placed in 4% paraformaldehyde (10% Formulin, Sigma, St. Louis, MO) for later histological verification of cannulae placement.

HPLC Analysis

The combined left and right punches from each brain region were homogenized in a solution of 195 μl of 0.1 M perchloric acid containing 5 μl of an internal standard, isoproterenol (Sigma) (1 μg/ml). Samples were then centrifuged at 12,500 rpm for 8 min in a SUREspin table-top microcentrifuge (Helena Laboratories, Beaumont, TX). The supernatant was removed from the vials and analyzed via high-performance liquid chromatography (HPLC). Concentrations of DA, DOPAC, and HVA were determined in each sample by HPLC coupled with electrochemical detection. Supernatants from each brain region were directly injected with a Beckmann System Gold 502 autosampler onto a Supelcosil LC-18-DB reverse phase microbore column (particle size, 5.1 μm^2, 250 × 2.1 mm). The mobile phase (pH 3.75) was pumped at 0.4 ml/min with a Shimadzu LC-6A pump and consisted of 0.1 M KH_2PO_4 (Fisher), 0.1 mM EDTA (Fisher), and 0.08 mM L-Heptane Sulfonate Sodium (Sigma). DA, DOPAC, and HVA were separated and detected with an ESA 7013 dual electrode analytical cell coupled to an ESA Coulochem II detector (guard cell potential: 400 mV; preoxidation electrode: 0 volts; oxidation electrode: 350 mV). All values were derived and analyzed from standard DA, DOPAC, and HVA concentration curves using a computerized data analysis program (Beckmann System Gold).

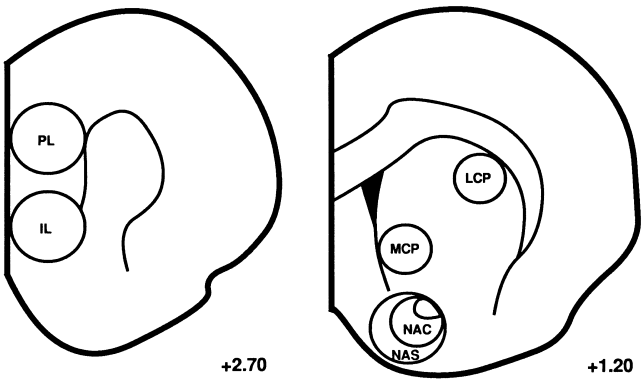

FIG. 1. Schematic depiction of brain regions used in microdissection experiment. An 840-mm diameter tube was used to dissect the nucleus accumbens core (NAC), medial caudate-putamen (MCP), and laterodorsal caudate-putamen (LCP) from a 1-mm coronal section. A 1600-mm diameter tube was used to dissect the nucleus accumbens shell (NAS), the infralimbic prefrontal cortex (IL), and the prelimbic prefrontal cortex (PL). The numbers at the lower left side of each section indicate the approximate distance of each coronal brain section from bregma [based on (21)].

Histological Verification of Cannula Sites

The posterior portion of each brain was frozen after removal of the cerebellum and cut on a cryostat. Coronal sections of 40 μm thickness were taken every 160 μm. Slices were collected from the dorsal hippocampus through the most posterior aspect of the brain. Sections were stained with neutral red. Cannula placement for the rats in the first (Fig. 2) and the second (Fig. 4) experiments was evaluated by visual inspection using light microscopy. Data obtained from animals with incorrect cannulae placement was removed from final statistical analyses.

Data Analysis

A two-way analysis of variance (ANOVA) was used to analyze data from the first experiment using time as a repeated measures factor and injection/infusion treatment as a between-group factor. The data derived from the preinfusion and postinfusion portions of the experiment were analyzed separately. Post hoc analysis was performed with Bonferroni *t*-tests, and $p < 0.008$ was maintained for significance in all analyses. Data in the microdissection experiment was analyzed in terms of DA turnover ratios (DOPAC/DA and HVA/DA). Student's *t*-tests were used to compare DA metabolism in each brain region between carbachol and ACSF animals. Alpha levels were set at $p < 0.01$.

RESULTS

Experiment 1: Acute Haloperidol Administration Blocks the Effects of Intrahippocampal Carbachol on Locomotor Activity

Animals in each group displayed an initial increase in locomotor activity after being placed in the testing cage which decreased over the remaining preinfusion period [tTime effect over preinfusion interval, $F(5, 255) = 111.8$, $p < 0.0001$, $n =$

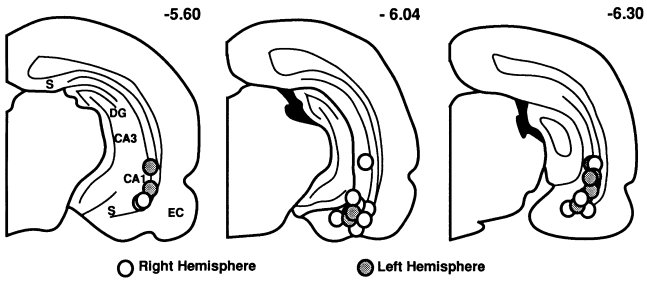

FIG. 2. Illustration of infusion sites from the first experiment. Most infusion sites were found around the CA1 region of the ventral hippocampus, although some of the injection sites were found in the ventral subiculum and entorhinal cortex. The numbers in the upper left side of each brain section indicate the approximate distance of each section from bregma [based on (21)]. Abbreviations: subiculum (S), dentate gyrus (DG), cornu ammons 3 and 1 (CA3 and CA1), entorhinal cortex (EC).

12–15] (Fig. 3). Intrahippocampal infusion of carbachol after saline pretreatment produced statistically significant increases in locomotor activity [overall group effect for postinfusion period, $F(3, 255) = 12.1$, $p < 0.0001$] (Fig. 3). Haloperidol pretreatment was found to block this effect. Comparisons between pretreatment + treatment conditions indicated that saline + carbachol treatment significantly elevated locomotor activity at each postinfusion time point in comparison to haloperidol + carbachol and haloperidol + ACSF treatment (Bonferroni *t*-test comparison, $p < 0.0024$–0.0001). At $t = 40$ and $t = 60$ min after intrahippocampal infusion, locomotor activity induced by saline + carbachol treatment was also found to be significantly greater than that observed after saline + ACSF treatment (Bonferroni *t*-test, $p < 0.0024$ at $t = 40$ minutes, $p < 0.005$ at $t = 60$ min). The histological evaluation indicated that the intrahippocampal infusion sites were found in the area of the ventral CA1 (and its dorsal and medial borders), as well as in the ventral subiculum, and entorhinal cortex (Fig. 2). Previous anatomical studies have demonstrated that these regions of the hippocampal formation and entorhinal cortex project to the NA and prefrontal cortex (7,24,28).

Experiment 2: Intrahippocampal Infusion of Carbachol Does Not Alter DA Turnover in the Nucleus Accumbens, Caudate-Putamen, and Prefrontal Cortex

The results of the first experiment indicated that DA plays an integral role in increased locomotor activity elicited by intrahippocampal carbachol. Given this finding, the second experiment was designed to determine whether hippocampal stimulation increases DA metabolism in DA-rich brain regions that receive hippocampal input (i.e., the NA shell and core, the medial caudate-putamen, and the infralimbic and prelimbic prefrontal cortices). The laterodorsal caudate-putamen was used as a control brain region, because it does not receive direct input from the hippocampus (12,17). The data indicate that intrahippocampal carbachol infusion did not significantly increase DA turnover in any of the brain regions examined (Table 1). Inspection of intrahippocampal infusion sites indicated that infusions were directed predominately at the same regions of the VH formation (Fig. 4) as observed in the first experiment.

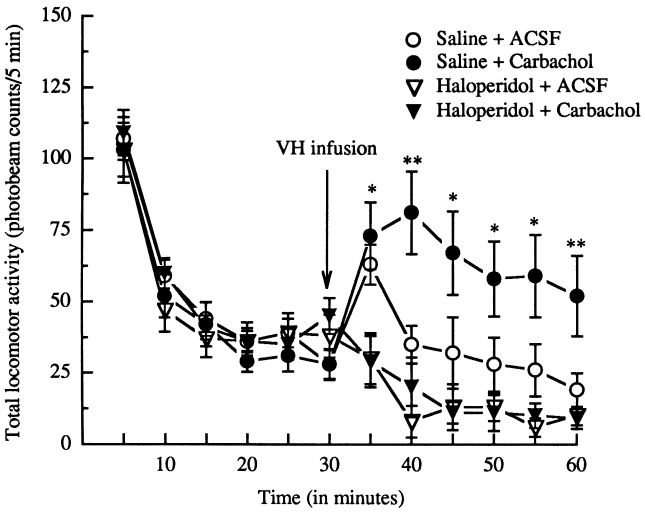

FIG. 3. Effect of VH infusion of carbachol (0.2 μl of 2 mg/ml solution) on locomotor activity. Each animal was placed in the test cage 30 min prior to VH infusion. Five minutes prior to VH infusion, animals were injected IP with haloperidol (0.1 mg/kg) or saline. Animals received bilateral infusion of carbachol or ACSF over 1 min to brain sites indicated in Fig. 2. Locomotor activity was increased after saline + carbachol treatment relative to haloperidol + carbachol and haloperidol + ACSF treatment at 35, 40, 45, 50, 55, and 60 min (as indicated by *), and relative to the saline + ACSF treatment at 40 and 60 min (as indicated by **). Locomotor activity data are presented as mean number of photobeam breaks + SEM. All differences between treatments are at $p < 0.005$–0.0001.

DISCUSSION

Many studies have attempted to elucidate the functional interaction between hippocampal and dopaminergic projections to subcortical and cortical brain structures. The impetus for these studies stems from the potential interaction of these brain regions in the regulation of motor behavior, emotion, reward, and psychosis (2,18,30). Thus far, hippocampal–dopaminergic interactions have been addressed using behavioral, biochemical, and electrophysiological methods; however, these interactions remain to be fully characterized. This study used two of these approaches to further define the behavioral consequences of hippocampal stimulation and how DA modulates this effect. Our results suggest that hippocampal stimulation elicits a DA-sensitive increase in locomotor activity, but that this effect is not a consequence of elevated DA metabolism in the forebrain and prefrontal cortex.

Many investigators have demonstrated that infusion of glutamate receptor agonists into the VH of animals elevates locomotor activity (1,31,33). One aim of the present study was to determine if elevations in locomotor activity could be achieved via stimulation of cholinergic receptors in the VH. For this purpose, carbachol, a well-known muscarinic receptor agonist, was utilized. Infusion of carbachol into the dorsal hippocampus is known to elevate locomotor activity (10,19), but studies have not yet addressed the effects of VH carbachol infusion on locomotor activity. The results obtained in the present study demonstrate that carbachol infusion into the VH increases locomotor activity. These findings, along with those from previous studies, suggest that increases in locomotor activity can be produced by activation of both cholinergic and glutamatergic receptors located on VH neurons.

Our behavioral experiment also suggests that the increased locomotor activity produced by hippocampal stimulation is modulated by DA. Haloperidol, a D_2 receptor antagonist, was found to block the effects of VH carbachol infusion on locomotor activity. Because haloperidol is a D_2 receptor antagonist, the results argue that D_2 receptor binding is necessary for hyperactivity elicited by VH stimulation, which is in agreement with previous studies (31). This conclusion, however,

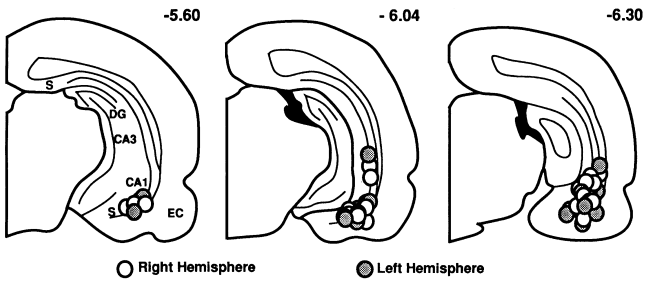

FIG. 4. Illustration of infusion sites in second experiment. See Fig. 2 for details.

TABLE 1

EFFECTS OF CARBACHOL INFUSION INTO VENTRAL HIPPOCAMPAL FORMATION ON DOPAMINE METABOLISM IN STRIATAL AND CORTICAL SUBREGIONS (MEAN RATIO ± SEM)

	DOPAC/Dopamine		HVA/Dopamine	
	Carbachol	ACSF	Carbachol	ACSF
Nucleus accumbens				
Shell	0.288 ± 0.032	0.277 ± 0.042	0.076 ± 0.015	0.063 ± 0.017
Core	0.374 ± 0.039	0.394 ± 0.055	0.082 ± 0.025	0.087 ± 0.010
Caudate-putamen				
Mediodorsal	0.149 ± 0.011	0.148 ± 0.009	0.058 ± 0.011	0.063 ± 0.031
Laterodorsal	0.143 ± 0.022	0.174 ± 0.034	0.071 ± 0.012	0.173 ± 0.083
Medial prefrontal cortex				
Infralimbic	0.485 ± 0.037	0.559 ± 0.093	0.923 ± 0.282	0.495 ± 0.142
Prelimbic	0.366 ± 0.062	0.311 ± 0.066	0.331 ± 0.042	0.366 ± 0.078

Infusion, tissue collection, and HPLC analysis procedures are described in the Method Section. Carbachol infusion into the VH did not alter the ratio of DOPAC/DA or HVA/DA in any of the brain regions studied. Data are presented as mean ratio ± SEM. ACSF–artificial cerebrospinal fluid.

should be considered tentative, because Yang and Mogenson (33) had previously demonstrated that intra-NA administration of the D_2 receptor agonist, quinpirole, also blocks elevations in locomotor activity elicited by chemical stimulation of the VH. It is possible that quinpirole's agonistic action at D_3 receptors (22,26), which inhibit locomotor activity when stimulated (29), may explain its suppressive action in the Yang and Mogenson study. It will be imperative in future research to test the effects of selective antagonists for DA receptor subtypes to better understand the contribution of each receptor subtype to heightened locomotor activity driven by hippocampal stimulation. Another issue for future consideration regards the site of action for haloperidol's effect on the increased locomotor activity observed after VH stimulation. Experiments wherein haloperidol is directly infused into a given brain region would provide more specific information as to its site of action. The NA would be a logical place to test for this effect, because investigators have already shown it to be a potential site of interaction between hippocampal and DA systems (33).

How DA mediates the elevation in locomotor activity observed after VH stimulation has yet to be determined. Dopamine may play a permissive role and only tonic activation of postsynaptic DA receptors may be required for increased locomotor activity elicited by VH stimulation. Alternatively, hippocampal stimulation may evoke increases in forebrain or cortical DA metabolism or release, which could elevate locomotor activity in a manner analogous to the hyperactivity associated with DA-elevating drugs, such as cocaine or amphetamine (3,15). The second experiment in the present study was designed to determine if intrahippocampal carbachol elevated DA turnover in key DA-rich brain regions. Dopamine turnover (i.e., ratios of DOPAC/DA or HVA/DA) was chosen as a measure of forebrain DA function because previous studies had demonstrated that it is a sensitive measure of environmental and pharmacological challenges to forebrain DA systems (9,14,20) and that it can be correlated with behavioral changes (14,20). The NA, prefrontal cortex, and medial caudate-putamen were chosen as regions of interest based on the projections from the VH to these brain regions (7,12,24,28). The laterodorsal caudate-putamen was utilized as a control tissue because there are few hippocampal fibers present in this brain region (12,17). Our data clearly show that carbachol infusion into the VH does not significantly alter DA turnover in the NA or any other brain regions. However, it should be noted that VH stimulation may produce other changes in DA function, namely increases in DA release, which could not be detected with our assay. Two recent studies (6,8) have demonstrated that electrical or chemical stimulation of the VH evokes the release of DA in the NA. These studies suggest that carbachol infusion into the VH could elevate DA release in the NA and warrant further biochemical considerations of subcortical DA function after VH carbachol infusion.

One of the underlying goals of this study was to develop an animal model of the hippocampal overactivity associated with psychiatric disorders, such as schizophrenia (11,23,25). We and others have shown that elevated activity in the VH of rats results in dramatic behavioral changes. Moreover, the present study demonstrates that an antipsychotic drug such as haloperidol can reverse these effects. It will be important in the future to determine if other antipsychotic drugs are effective in preventing the increased locomotor activity observed after VH stimulation. Such studies may suggest that the suppression of increased locomotor activity produced by VH stimulation can serve as a useful indicator of a new compound's antipsychotic potential.

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