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Serotonergic Stimulation of the Ventrolateral Striatum Induces Orofacial Stereotypy

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YEGHIAYAN, S. K. AND A. E. KELLEY. *Serotonergic stimulation of the ventrolateral striatum induces orofacial stereotypy.* PHARMACOL BIOCHEM BEHAV 52(3) 493-501, 1995.—Dopaminergic (DA) stimulation of the ventrolateral striatum produces a syndrome of intense orofacial stereotypies. In addition to dopaminergic projections from the substantia nigra, the striatum receives serotonergic (5-HT) inputs arising from the raphe nuclei. To assess the putative role of striatal 5-HT in orofacial movements, serotonin (0, 0.2, 2, 10, 20 μg/1.0 μl) was infused into the ventrolateral striatum and behaviors were recorded using a time-sampling procedure. Serotonin produced a dose-dependent, site-specific increase in stereotyped orofacial behaviors. Infusion of selective 5-HT receptor agonists or uptake inhibitors did not produce the orofacial syndrome and pretreatment with either selective or nonselective 5-HT receptor antagonists did not block the 5-HT induced stereotypy. In contrast, pretreatment with DA receptor antagonists completely abolished the 5-HT induced repetitive orofacial movements, providing evidence for a 5-HT/DA interaction at this site. Moreover, depletion of DA with a combination of reserpine and α-methyl-*p*-tyrosine markedly decreased the stereotyped behaviors induced by 5-HT microinfusion. These data provide evidence for an interaction between 5-HT and DA in the striatum at presynaptic DA terminals. It is hypothesized that 5-HT may cause release of DA via reversal of the DA transporter. This syndrome may provide an animal model for some aspects of obsessive-compulsive disorder, because current theories of this disorder implicate 5-HT dysfunction in the basal ganglia.

Serotonin Dopamine Striatum Orofacial stereotypy Compulsive behaviors

THE VENTROLATERAL sector of the striatum (VLS) appears to be critically involved in oral motor behavior. Because of the high density of dopamine (DA) nerve terminals in this site, past investigations have focused on manipulations of this neurotransmitter. Stimulation of DA in the VLS with agents such as *d*-amphetamine has been found to produce a syndrome of intense orofacial movements (32). Treated animals engage in perseverative licking, biting, and gnawing with a rapid induction and cessation of these behaviors; the syndrome generally begins and ends within 30 min. Further experiments have shown that stimulation of both D_1 and D_2 receptors are required for full expression of the syndrome (22). Oral stereotypies elicited with dopaminergic stimulation are specific to the ventrolateral sector of the striatum. Microinjection of DA agonists to other striatal subregions does not lead to the compulsive licking and biting behaviors observed with VLS cannulae placements (23,33).

Although DA clearly plays a role in oral movements, it is important to consider the possible role of other neurotransmitters in this region. For example, there are dense serotonergic projections arising from the midbrain raphe nuclei, especially the dorsal nucleus, which innervate the striatum (57,61,67). Ternaux and colleagues (64) have identified the ventrocaudal areas of the rat striatum as among the areas of highest serotonin (5-HT) density in the brain. Similarly, a slight rostral-caudal and dorsal-ventral gradient has been noted, where 5-HT concentrations are higher in more caudal and ventral sections of the striatum (5,57). Furthermore, Beal and Martin (5) found 5-HT concentrations to be highest in the ventromedial areas of the striatum, with the second highest area of concentration being the ventrolateral striatum, and the least represented areas being the dorsomedial and dorsolateral striatum. Moreover, several subtypes of the 5-HT receptor have been identified within the striatum. Receptors of the 5-HT_1 and 5-HT_2 classes have been found in this structure and, more recently, the existence of the 5-HT_3 receptor in this site was confirmed (8,35,72).

Interaction between the 5-HT and DA systems has been

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demonstrated by many researchers, but the precise nature of the relationship in the striatum remains to be clarified. Although much research has accumulated suggesting an inhibitory role of 5-HT on DA function in the striatum (2,36,38,66), conflicting findings of facilitation of DA release by 5-HT have also been reported. For example, using microdialysis techniques, it has been demonstrated that infusion of 5-HT and various 5-HT_1 agonists produced dose-dependent increases in DA release in the anterior striatum (7). A facilitatory effect of 5-HT on [^{3}H]DA release in slices from rat accumbens and striatum has been demonstrated as well (31,44,45,71). Behavioral experiments do not shed light on these conflicting findings; for example, 5-HT antagonists reduce DA-mediated behavior (17), yet striatal serotonergic lesions are reported to enhance amphetamine-mediated stereotypy (16).

The stereotyped motor responses observed following dopaminergic stimulation of the striatum are reminiscent of the perseverative motor actions associated with obsessive-compulsive disorder (OCD). For example, sufferers of OCD are compelled to repeat grooming and checking routines, two common behaviors observed in this disorder, well beyond any useful purpose that they may serve. An interesting point to note about the symptoms of OCD is that many of the apparently purposeless behaviors that sufferers exhibit are fragments of normal daily behaviors. Similarly, the oral stereotypies noted in rats also occur normally, but are unusual in their repetitive and intense nature.

Currently, the only drugs that are successful in decreasing OCD symptoms are inhibitors of 5-HT uptake (1,24,26,47). Thus, abnormalities in 5-HT function have been implicated in OCD, although the precise nature of this dysfunction remains unknown (6,50,73). In addition to a putative serotonergic involvement in this disorder, a second major theory of OCD implicates basal ganglia dysfunction (42). For example, positron emission tomography (PET) demonstrates an increased metabolic rate for glucose in the caudate nuclei as well as the frontal cortex of OCD patients (3). In view of these findings, it is possible that abnormal 5-HT function or abnormal interactions between 5-HT and other striatal transmitters, are associated with the symptoms of OCD. Very few animal experiments, however, have been performed in an effort to link the striatum, 5-HT, and stereotypy as a potential model for OCD. Therefore, the present investigation assesses the behavioral effects of striatal infusion of 5-HT.

METHODS AND MATERIALS

Subjects, Housing Conditions, and Surgery

Male, Sprague-Dawley rats (N = 94) weighing 300–350 g (Charles River Laboratories, Wilmington, MA) were housed individually in clear plastic cages with free access to food and water. The colony was illuminated on a 12L : 12D cycle, with lights on 0700–1900 h. On arrival in the laboratory, rats were habituated to handling to minimize stress during testing. For stereotaxic implantation of chronic indwelling cannulae, rats were injected intraperitoneally (IP) with sodium pentobarbital (65 mg/kg) and placed in a stereotaxic apparatus (David Kopf Instr., Tujunga, CA). The coordinates for the ventrolateral striatum (A-P: +1.8 from bregma, L-M: ±4.0 from midline, D-V: −4.7 from skull) and for the dorsolateral striatum (A-P: +2.7 from bregma, L-M: ±3.0 from midline, D-V: −3.4 from skull) were based on the atlas of Pellegrino and Cushman (46). Stainless steel guide cannulae (23 ga) were aimed 2.5-mm above the site of injection, and were affixed to the skull with a light-curable dental resin. Wire stylets were placed in the guides to prevent occlusion of the guide cannulae. All behavioral testing began approximately 5 days after surgery.

Microinjection Procedure

For intracerebral (IC) injections, bilateral injector cannulae (30 ga) were attached to polyethylene tubing (PE-10), which was connected to a microdrive pump (Harvard Apparatus, So. Natick, MA). For an infusion, the injector cannulae were lowered through the guide to the desired site of infusion. The volume infused was either 0.5 μl or 1.0 μl at a rate of 0.392 μl/min. Initial experiments utilized the lower volume; in later experiments, the greater volume was used to maximize spread of the injectate. One additional minute was allowed for diffusion time and replacement of the stylets. One day before experimental infusions, the rats were given a preliminary vehicle infusion to adapt them to the injection procedure. Isotonic saline was used as the vehicle solution for drug injection. Treatments were always administered in a counterbalanced order. In all studies using 5-HT, as well as the studies using 2-Me-5-HT, fluoxetine, and zimelidine, the monoamine oxidase inhibitor, pargyline (25 mg/kg IP) was administered to prevent rapid degradation of 5-HT. Pargyline was injected 30 min prior to drug infusion into the brain.

Behavioral Testing

Immediately after IC infusion, rats were returned to their home cages. A trained observer, blind to treatment, then recorded the behavior for 1 h (with the exception of one part of Experiment 1 in which animals were tested for 4.5 h). There were 12 1-min observation periods, spaced every 5 min over the test session. Oral behavior categories were defined as follows: *lick*, licking any part of cage; *bite*, biting any part of cage; *gnaw*, gnawing any part of body (self-gnawing); *mouth movements*, mouth movements not directed toward cage or body; *taffy-pull*, repetitive paw-to-mouth movements; and *head-down sniff/paw*, repetitive snout and paw movements directed down through grid of cage. Other behaviors recorded included *still, loco, rear*, and *groom*. Behaviors that occurred during each 1-min observation period were given a score of 1; a 0 was recorded if the behavior did not occur. A combined score termed orofacial stereotypy was obtained by summing individual scores for lick, bite, self-gnaw, taffy-pull, and head-down sniff/paw. A total score for each category over the entire session was obtained by summing the scores of the individual time bins.

Drugs

The following drugs were used in these experiments: 5-hydroxytryptamine hydrochloride (serotonin hydrochloride), (±)-1-(4-iodo-2,5-dimethoxyphenyl)-2-aminopropane hydrochloride (DOI), (±)-8-hydroxy-N,N-dipropylaminotetralin hydrobromide (8-OH-DPAT), 1-(3-chlorophenyl)piperazine dihydrochloride (mCPP dihydrochloride), 2-Me-5-HT, zimelidine dihydrochloride, mianserin hydrochloride, ritanserin, methysergide maleate, R(+)-SCH-23390 hydrochloride, S(−)-propranolol hydrochloride, 1-phenylbiguanide, and 3-tropanyl-3,5-dichlorobenzoate (MDL-72222), and reserpine. These compounds were obtained from Research Biochemicals, Intl. (Natick, MA). The following compounds also were used in these experiments: raclopride (Astra AB, Södertalje, Sweden), α-methyl-DL-*p*-tyrosine methyl ester (AMPT, Sigma Chemical Co., St. Louis, MO), ondansetron (GR38032F,

Glaxo Group Research, Middlesex, UK), RU24969 (Roussel-Uclaf, Paris, France), fluoxetine (Eli Lilly, Indianapolis, IN), pargyline (Sigma Chemical Co., St. Louis, MO). Serotonin and 2-Me-5-HT were dissolved in 0.9% NaCl. Ritanserin was dissolved in Tween 80 and distilled water. Reserpine was dissolved in glacial acetic acid and distilled water. All drugs used for brain injections were dissolved in saline. To dissolve fluoxetine, the solution was heated lightly. MDL-72222 was dissolved in glacial acetic acid and distilled water and the pH was then adjusted to 5.5. All other drugs were dissolved in distilled water. At least 1 day elapsed between all drug treatments.

Histological Analysis

All infusion sites were verified by histological analysis of cannulae tracks. At the end of an experiment, animals were deeply anaesthetized with sodium pentobarbital and perfused transcardially with isotonic saline followed by 10% formalin. Brains were removed and subsequently frozen and sectioned with a microtome. Cresyl-violet stained sections were examined using light microscopy and the location of cannulae tracks was determined. Placements were subsequently represented on drawn reconstructed sections.

Data Analysis

For the behavioral ratings, the mean total score for each category was analyzed for differences between groups or treatments. For paired comparisons within groups (drug vs. vehicle), the Wilcoxon matched-pairs signed-ranks test was utilized. If multiple comparisons were carried out within an experiment (e.g., vehicle vs. a particular drug dose), a Bonferroni adjustment was applied to set a more stringent significance criterion (52). In this case, the conventional alpha level, 0.05, was divided by the number of pairwise comparisons.

Experimental Design

Experiment I: 5-HT in ventrolateral striatum and dorsolateral striatum. In this investigation, serotonin (0, 0.2, 2, 10, 20 μg/1.0 μl) was infused into the VLS (n = 6) and behavior was observed. To test the anatomical specificity of any observed effects, similar infusions were carried out in the dorsolateral striatum (DLS) (n = 6). For purposes of comparison, another group of rats (n = 8) was injected with dopamine (0, 2, 10, 20 μg/1.0 μl) in the VLS (these rats also received a pargyline pretreatment). All experiments were conducted with the experimenter blind to treatment. In this repeated measure design, all rats received all doses, and at least 1 day elapsed between test sessions.

Experiment II: Direct and indirect 5-HT agonists in ventrolateral striatum. In this series of experiments, the behavioral effects of VLS infusions of various direct and indirect agonists were assessed. The first group of rats (n = 8) received one injection of the 5-HT_{1A} agonist, 8-OH-DPAT (4 μg/0.5 μl). A second group (n = 7) received one injection of the 5-$HT_{1B/1C/2}$ agonist, mCPP (20 μg/0.5 μl). A third group (n = 7) received one injection of the selective 5-HT_3 agonist, 1-PBG (20 μg/1.0 μl). In a fourth group of animals (n = 8), three counterbalanced injections were given. These rats received the 5-HT uptake inhibitors, fluoxetine (20 μg/1.0 μl) or zimelidine (20 μg/1.0 μl), or vehicle. A fifth group of rats (n = 8) received four injections: the 5-HT_{1B} agonist, RU24969 (4 μg/1.0 μl), the 5-$HT_{2/1C}$ agonist, DOI (10 μg/1.0 μl), the 5-HT_3 agonist, 2-Me-5-HT (15 μg/1.0 μl), or vehicle. Relatively high doses were purposely chosen, based on assessment of available literature, to maximize a potential behavioral effect. For example, the dose of 8-OH-DPAT was considerably higher than active doses used in previous microinjection studies (11,25). For drugs in which IC injection data were not available, a dose approximately equimolar to the active 5-HT dose was given.

Experiment III: 5-HT and DA antagonists. In the first study, animals were administered intra-VLS 5-HT (30 μg/1.0 μl) and the effects of pretreatment with either a 5-HT or DA antagonist were analyzed. Animals (n = 6) were administered either the nonselective 5-HT antagonist, methysergide (7.5 mg/kg, IP, 60-min pretreatment), the selective D_1 antagonist, SCH-23390 (0.1 mg/kg, IP, 40-min pretreatment), the selective D_2 antagonist, raclopride (1.0 mg/kg, IP, 40-min pretreatment), or no antagonist pretreatment. In the second series of studies, which examined the effects of more selective 5-HT antagonists, 5-HT was infused into the VLS in a dose of 15 μg/1.0 μl. The first group of animals (n = 7) received the 5-HT_{1B} antagonist, propranolol (0, 5, 10, 20 mg/kg IP, 20-min pretreatment). A second group of rats (n = 7) received the 5-HT_{1C} antagonist, mianserin (0, 0.02, 0.2, 2.0 mg/kg, IP, 20-min pretreatment) and the 5-$HT_{2/1C}$ antagonist, ritanserin (1.0 mg/kg, IP, 20-min pretreatment). In a third study, rats (n = 8) received a selective 5-HT_3 antagonist, ondansetron (0, 0.003, 0.03, 0.3 mg/kg, IP, 45-min pretreatment). Finally, one group of animals (n = 7) received the 5-HT_3 antagonist, MDL-72222 (3 mg/kg, IP, 20-min pretreatment). In all cases, antagonist doses were counterbalanced across test session and at least 1 day elapsed between drug treatments. The dose range and pretreatment times of the antagonists were chosen to maximize receptor occupancy at the time of the IC injection, and were based on previous work in the literature (28,41,58,63).

Experiment IV: Presynaptic DA depletion. In this study, rats (n = 8) were infused with 5-HT (15 μg/1.0 μl) and their behavior was recorded. One day later, they were administered the amine vesicle-depleting agent, reserpine (0.75 mg/kg, IP). Twenty-four hours later, the reserpine treatment was followed by the catecholamine synthesis inhibitor, α-methyl-p-tyrosine (60 mg/kg, IP). After 2 h, animals were infused with 5-HT (15 μg/1.0 μl) into the VLS and their behavior was recorded again. After a recovery period of 4 days, 5-HT (15 μg/1.0 μl) was infused again and behavior was recorded. Two days later, the DA-depleting treatments were then repeated in the same group of rats using a higher dose of reserpine (1.0 mg/kg, IP) and the response to 5-HT was again recorded. A final treatment of 5-HT was administered 4 days later and behavior was again assessed. It has been demonstrated that tissue catecholamine levels return to normal within 4 days following higher doses of reserpine than used in these studies (56).

RESULTS

Behavioral Effects of 5-HT Infusion Into Ventrolateral Striatum

As shown in Fig. 1A, microinfusion of 5-HT into the VLS produced a dose-dependent increase in orofacial stereotypy. Treated rats showed continuous sniffing and gnawing behaviors that generally began after 40 min and continued beyond 1 h. The animals were observed most often to be engaged in either noninjurious self-gnawing or repetitive snout and paw movements directly through the bars of the cage bottom. The time course of this effect is shown in Fig. 1B. For purposes of clarity, scores collected every 5 min were summed over 30 min, for the time-course graph. It can be observed from the figure that maximal stereotypy did not occur until 30–60 min following infusion and subsided approximately 4 h later. Infusion

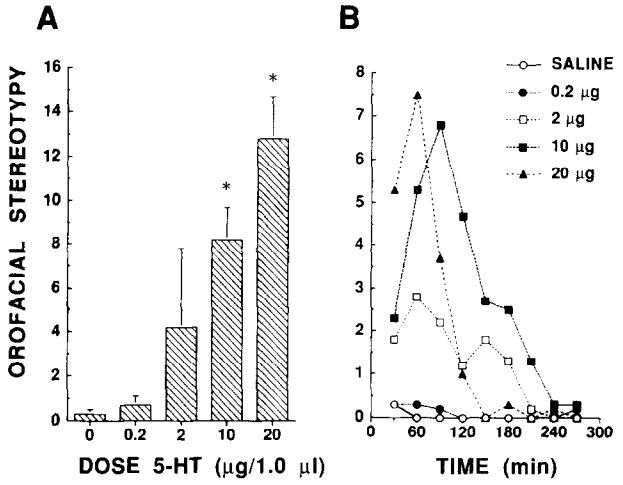

FIG. 1. Behavioral effect of 5-HT infusion into VLS. (A) Dose-dependent increase in orofacial stereotypy during a 60-min session ($n = 6$). Values are means ± SEM. *$p < 0.02$, Wilcoxon matched-pairs signed-ranks test. (B) Time course of 5-HT-induced orofacial stereotypy. Values represent mean scores.

of 5-HT into the DLS did not produce stereotyped orofacial behaviors, nor did any observable alterations in behavior occur (data not shown). The mean orofacial stereotypy score following infusion of the highest dose of 5-HT into the DLS was 0.7 ± 0.5. Table 1 shows that DA infused into the VLS also elicited orofacial stereotypy, confirming previous findings from this laboratory (22).

Effects of Direct and Indirect 5-HT Agonists

Infusion of various 5-HT agonists into the VLS had no effect on any category of behavior observed. As Table 2 shows, intra-VLS infusion of agonists that are selective for the 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, 5-HT_2, and 5-HT_3 receptors did not elicit the orofacial stereotypy observed following infusion of the endogenous neurotransmitter, 5-HT. Moreover, treatment with relatively high doses of the indirect agonists, fluoxetine and zimelidine, also did not produce changes in oral behavior.

Pretreatment With 5-HT or DA Antagonists

Systemic administration of antagonists that are selective for the 5-HT_{1B}, 5-HT_{1C}, 5-$HT_{2/1C}$, and 5-HT_3 receptors did not decrease the 5-HT elicited orofacial stereotypy, as shown in Table 3. The nonselective 5-HT antagonist, methysergide (7.5 mg/kg), also did not affect expression of the behaviors induced with 5-HT infusion into the VLS (see Fig. 2). In contrast, SCH-23390 (0.1 mg/kg) and raclopride (1.0 mg/kg), reduced or abolished orofacial stereotypy elicited with 5-HT infusion into the VLS (see Fig. 2). Following DA antagonist pretreatment, behavior appeared similar to saline-infused animals.

TABLE 1

ORAL BEHAVIOR FOLLOWING BILATERAL INFUSION OF DOPAMINE INTO RAT VENTROLATERAL STRIATUM

Dose (µg)	Orofacial Stereotypy
0	0.1 ± 0.1
2	8.9 ± 1.7
10	12.4 ± 1.5
20	12.6 ± 2.1

Values for orofacial stereotypy are mean scores ± SEM (60-min test). *$p < 0.02$ by Wilcoxon matched-pairs signed-ranks test.

TABLE 2

ORAL BEHAVIOR FOLLOWING BILATERAL INFUSION OF SELECTIVE AND NONSELECTIVE 5-HT AGONISTS AND 5-HT UPTAKE INHIBITORS INTO RAT VENTROLATERAL STRIATUM

Drug	Receptor	Dose (µg)	Orofacial Stereotypy
5-HT	5-$HT_{1,2,3}$	20	7.2 ± 1.5*
8-OH-DPAT	5-HT_{1A}	4	0
RU-24969	5-HT_{1B}	4	0.1 ± 0.1
mCPP	5-$HT_{1B\text{-}C/2}$	20	0
DOI	5-$HT_{2/1C}$	10	0
2-Me-5-HT	5-HT_3	15	0
1-PBG	5-HT_3	20	0.7 ± 0.7
Fluoxetine	Uptake blocker	20	0
Zimelidine	Uptake blocker	20	0.4 ± 0.3

Values for orofacial stereotypy are mean scores ± SEM. *$p < 0.02$ by Wilcoxon matched-pairs signed-ranks test.

*Effect of DA Depletion Using Reserpine and α-Methyl-*p*-tyrosine*

Because DA antagonists were highly effective in blocking the 5-HT mediated effect, it was of interest to investigate whether the DA system was being influenced presynaptically or postsynaptically. As shown in Fig. 3, pretreatment with the amine depleting drugs, reserpine and AMPT, produced a significant reduction in 5-HT elicited orofacial behaviors. Following a drug-free period of 4 days, the 5-HT induced behaviors were elicited again, only to decrease with a second series of DA-depleting treatments. Finally, after another 4-day recovery period, the 5-HT elicited behaviors again returned.

TABLE 3

EFFECT OF SYSTEMIC ADMINISTRATION OF SELECTIVE 5-HT ANTAGONISTS ON OROFACIAL BEHAVIORS INDUCED BY 5-HT INFUSIONS INTO VLS

Drug	Receptor	Dose (µg/kg IP)	Orofacial Stereotypy
Propranolol	5-HT_{1B}	20	7.6 ± 1.9
Mianserin	5-HT_{1C}	2.0	8.1 ± 1.5
Ritanserin	5-$HT_{2/1C}$	1.0	9.9 ± 1.5
Ondansetron	5-HT_3	0.3	9.9 ± 1.8
MDL 72222	5-HT_3	3	9.9 ± 1.1

5-HT (15 µg/1.0 µl) was infused into ventrolateral striatum (VLS) bilaterally. Stereotypy scores shown are means ± SEM following the highest dose of antagonist. Scores shown were not significantly different from those following VLS 5-HT infusions without antagonist pretreatment (8.7 ± 1.5).

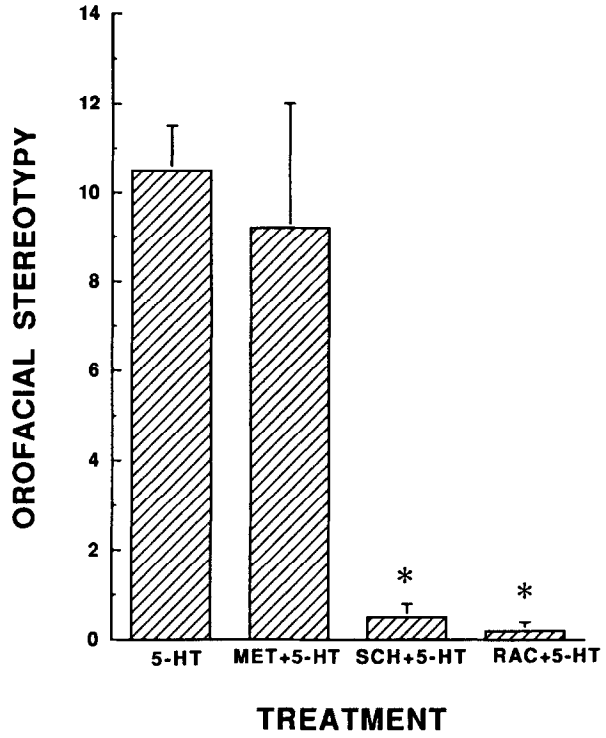

FIG. 2. Effect of systemic administration of a nonselective 5-HT antagonist methysergide (MET; 7.4 mg/kg), D_1 antagonist SCH-23390 (SCH; 0.1 mg/kg), or D_2 antagonist raclopride (RAC; 1.0 mg/kg, IP) on stereotypy induced by 30 μg of 5-HT infused bilaterally into ventrolateral striatum (VLS). Values represent mean scores ± SEM (n = 6). *$p < 0.02$.

Histologic Analysis

Figure 4 shows schematic histologic drawings of cannulae tracks from representative animals. Shown are examples from the group of animals from the third and fourth experiments. An example is also provided from the dorsolateral striatal group, in which 5-HT infusions did not result in stereotypy.

DISCUSSION

The present results demonstrate that infusion of 5-HT into the VLS of the rat induces a dose-dependent increase in perseverative orofacial behaviors. The syndrome appears to be site-specific, as injections of 5-HT into the DLS did not produce orofacial behaviors. In previous studies, it has been determined that this particular striatal region is involved in the control of orofacial movements (22,32,33,34). For example, infusion of DA or DA agonists into this region induces intense oral stereotypy, as confirmed in this study. Although systemic administration of 5-HT agonists has been reported to cause some forms of motor stereotypy [e.g., head-weaving and forepaw treading (20)], DA-like orofacial stereotypy has not been reported. The finding that DA antagonists blocked the 5-HT induced behavioral effect provides strong evidence that DA is involved. As is true for DA-mediated stereotypy (12,13, 22,68), synergistic activation of both D_1 and D_2 DA receptor types appears to be essential for expression of 5-HT mediated stereotypy. The results suggest that 5-HT–DA interactions may play an important role in striatal control of motor function. Despite the commonly held view that 5-HT exerts an inhibitory influence on DA (16,69,70), the present findings indicate that in some circumstances 5-HT may activate the DA system.

It is notable that of all the 5-HT agonists tested in the present study, only the endogenous transmitter itself was capable of producing the orofacial syndrome. Infusion of agonists that are selective for the 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, 5-HT_2, and HT_3 receptor sites did not produce the behavioral syndrome, nor did selective antagonists for the 5-HT_{1B}, 5-HT_{1C}, 5-HT_2, and 5-HT_3 receptors decrease the 5-HT induced stereotypy. This lack of ability of 5-HT antagonists to reduce the stereotypy is particularly surprising. It was originally expected that 5-HT_{1B} or 5-HT_3 sites might play a role in 5-HT mediated stereotypy. For example, 5-HT_{1B} receptors appear to be involved in certain forms of behavioral activation, such as hyperactivity. Systemic administration of agonists for this receptor elicit hyperactivity (51,65), and 5-HT_{1B} antagonists block the hyperactivity induced by indirect 5-HT agonists (14,15). Moreover, certain 5-HT agonist drugs induce "purposeless chewing" when given systemically; this effect seems to be dependent on a 5-HT_{1B} site (62). However, in the present case, it was clear that the 5-HT_{1B} antagonist (propranolol) had no effect on 5-HT induced stereotypy, nor was the 5-HT_{1B} agonist RU24969 capable of inducing the behavior. Another likely candidate was the 5-HT_3 receptor, since there is some evidence that 5-HT_3 antagonists can attenuate DA-mediated behaviors (19,63). However, stereotypy induced by 5-HT infusion into the VLS was not blocked by 5-HT_3 antagonists (ondansetron

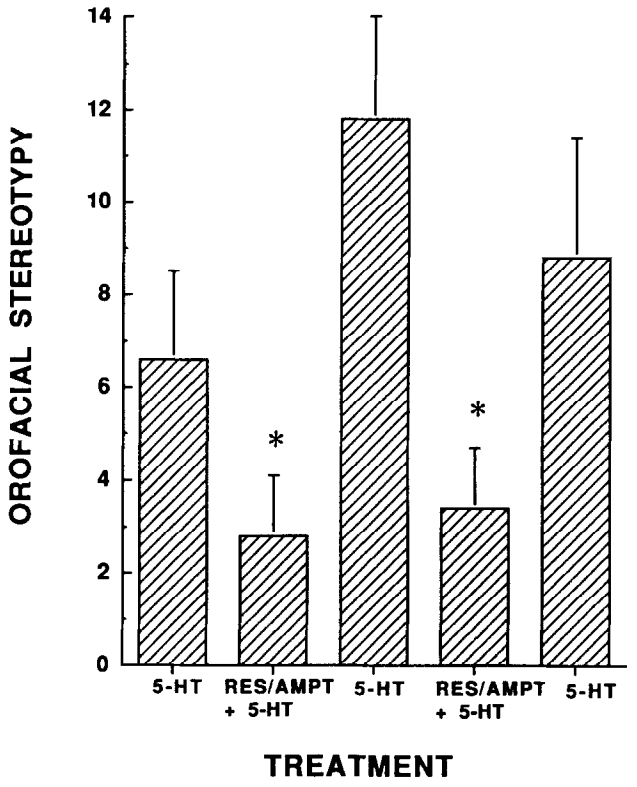

FIG. 3. Effect of DA-depleting treatment with reserpine (RES; 0.75 mg/kg in the first experiment and 1.0 mg/kg in the second) and α-methyl-p-tyrosine (AMPT; 60 mg/kg, IP) on orofacial stereotypy elicited by infusion of 5-HT (15 μg/1.0 μl) into VLS bilaterally. Values represent mean scores ± SEM (n = 8). *$p < 0.02$.

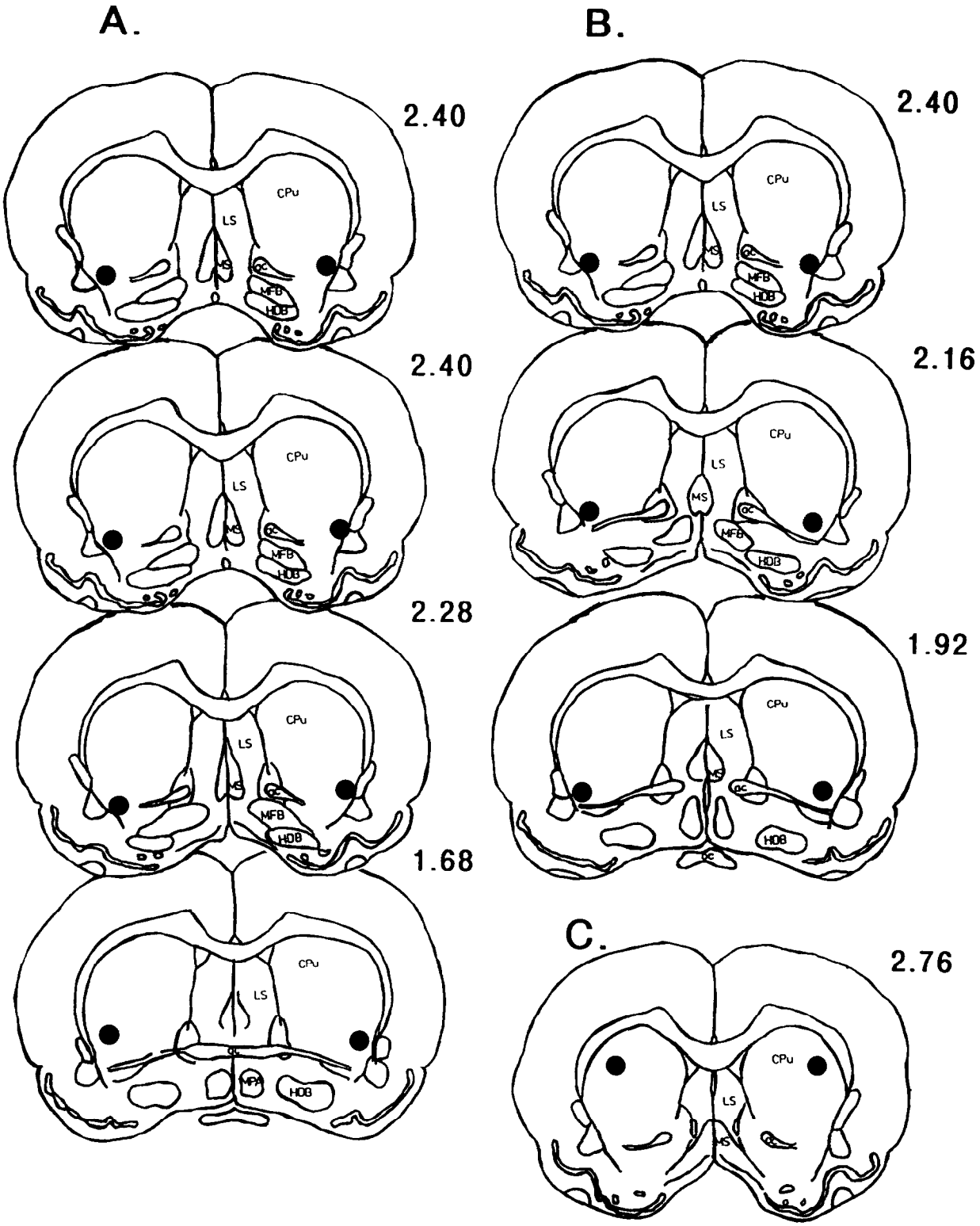

FIG. 4. Histologic reconstructions from representative animals in the third (A) and fourth (B) experimental groups, showing placement of cannulae in rat ventrolateral striatum (VLS). (C) An example from a site-specificity experiment in which cannulae were placed bilaterally in dorsolateral striatum (DLS). Numbers indicate distance from bregma, in millimeters.

and MDL-72222), nor was it elicited by 5-HT_3 agonists (2-Me-5-HT and 1-phenylbiguanide).

The apparent lack of 5-HT receptor involvement and the near total blockade of the syndrome with DA antagonists suggests a mechanism of interaction between 5-HT and DA in this region that does not involve 5-HT receptors, but may involve release of DA by 5-HT. There is ample evidence that application of 5-HT to the striatum or nucleus accumbens increases presynaptic release of DA. In studies using slice preparations or in vivo microdialysis, it has been shown that 5-HT increases extracellular DA levels (7,9,10,21,31,45,71). The notion of 5-HT induced DA release is consistent with our findings demonstrating that an intact DA system is required for the occurrence of 5-HT induced stereotypy. Depletion of presynaptic DA stores with reserpine and AMPT significantly decreased the oral stereotypy levels following 5-HT infusion into the VLS. There is little agreement, however, concerning the mechanism responsible for the 5-HT–DA interaction. Several investigations have implicated the 5-HT_3 receptor. For example, Blandina and colleagues (9,10) determined that application of 5-HT to rat striatal slices, as well as the 5-HT_3 agonists 2-Me-5-HT and 1-phenylbiguanide, induced spontaneous release of DA. The DA releasing effect of these compounds was attenuated following perfusion of the striatal slices with 5-HT antagonists. Similar findings were reported for the nucleus accumbens (18). In contrast, several studies have reported that 5-HT induced release of DA was not blocked by a number of serotonin antagonists, including compounds acting at the 5-HT_2 and 5-HT_3 sites (31,44,71); however, in all three studies the effect was blocked by DA uptake blockers such as nomifensine. To account for these findings it has been proposed that 5-HT may induce DA release via a carrier-mediated mechanism (exchange diffusion). Serotonin may enter the presynaptic DA terminal via attachment to the DA transporter, and cause displacement of DA from vesicular stores. This displaced DA is then carried out of the terminal by the DA transporter. There is growing evidence for a number of neurotransmitter systems in which release can occur through membrane carriers responsible for transmitter uptake (37). In support of this theory, it has been established that DA terminals can take up labeled 5-HT (55,64). If the DA transporter is involved in 5-HT induced oral stereotypy, one would predict that pretreatment with DA uptake blockers would reduce the 5-HT mediated behavior. Indeed, preliminary data using the DA uptake inhibitor, GBR-12909, have provided support for this hypothesis (unpublished findings). Whether 5-HT elicits DA release via stimulation of the 5-HT_3 receptor, reversal of the DA carrier, or perhaps via both mechanisms, remains to be clarified. One study suggests that both receptor- and nonreceptor-mediated mechanisms may be at work; in striatal slices, 1-phenylbiguanide induced DA release, an effect that was not blocked by 5-HT_3 antagonists, but was reduced by the addition of nomifensine to the perfusate (54).

If binding to the DA transporter is the initial step in this process, the structural requirements of the molecule appear highly specific. The 5-HT analog, 2-Me-5-HT, which differs from the endogenous neurotransmitter only by one methyl group, did not produce the orofacial syndrome. Future efforts should be aimed at determining the necessary structural characteristics of compounds capable of eliciting orofacial stereotypy following intra-VLS infusion. The possibility of synergistic effects between 5-HT receptor subtypes may also account for the 5-HT specific behavioral effect and should be explored in the future.

The orofacial syndrome elicited by 5-HT is clearly dose-dependent; however, the doses required to induce strong stereotypy are rather high. Moreover, the fact that the syndrome was not observed following infusion of the selective 5-HT uptake inhibitors, fluoxetine and zimelidine, suggests that blockade of 5-HT uptake may not result in sufficiently high synaptic levels to induce the syndrome. In many cases with IC microinjections, relatively high concentrations of the naturally occurring neurotransmitter (compared with synthetic drugs) are often needed to observe behavioral effects, because the inactivation processes (uptake, enzymatic degradation) associated with the transmitter molecule are very powerful. The active dose range for both 5-HT and DA was similar, suggesting that whether the site of action is presynaptic or postsynaptic, high concentrations are required for behavioral effects. Further, our unpublished observations have shown that without coadministraton of pargyline, even with high doses of 5-HT, the syndrome does not occur. Additionally, although the concentration of the injectate is known, the ultimate concentration at the synapse following diffusion is undoubtedly much lower. Although the significance of the 5-HT related motor syndrome awaits further study, for these reasons, the use of high doses of endogenous transmitter does not imply lack of physiological relevance.

It is noteworthy that 5-HT elicited orofacial stereotypy is similar to DA-mediated oral behaviors, with the exception of the time-course. While the DA-induced syndrome has a relatively rapid onset (32), the 5-HT mediated effect is delayed in comparison. In addition, we have also observed that intra-accumbens infusion of 5-HT produces a long-lasting locomotor hyperactivity that is delayed in onset (unpublished observations). The mechanism underlying this delay is at present unknown; however, it may involve long-term or indirect effects of 5-HT. The fact that there is a delay lends support to the indirect mechanism of interaction described above; for example, the temporal characteristics of 5-HT induced reversal of the DA transporter may be quite different from conventional agonist-receptor interactions.

Finally, the clinical relevance of these data should be considered. The stereotyped orofacial behaviors observed following serotonergic stimulation of the VLS may model certain aspects of OCD. Brain imaging techniques have revealed abnormalities in the basal ganglia and frontal cortex in OCD (3,39,53). Moreover, normalization of these variations is observed following either behavioral therapy or drug treatment (4). Based on findings such as these, cerebral cortical and basal ganglia structures may both be involved in the abnormal behaviors and thoughts of OCD patients (42,49,59). It has been suggested that dysfunction of regulatory neuronal mechanisms or abnormal inhibition within the "fronto-striato-pallido-thalamo-frontal loop" may account for the compulsive behaviors observed in OCD patients (42). It is also generally agreed that abnormalities in brain 5-HT systems may be involved in OCD, because specific 5-HT uptake inhibitors such as clomipramine, fluoxetine, and fluvoxamine are most effective in reducing the symptoms of the disorder. Although 5-HT dysfunction is implicated in OCD, there is little agreement as to the precise abnormality. Uptake inhibitors acutely increase synaptic levels of 5-HT; however, the neuronal basis of the long-term, therapeutic effect is unclear. Some studies suggest that overactivity of the 5-HT system is associated with OCD. Administration of the direct 5-HT agonist mCPP to untreated OCD patients markedly worsens their symptoms, an effect that is blunted by prior treatment with clomipramine (29, 43,73). It also has been suggested that an imbalance in 5-HT–DA interactions may also play a role in the pathophysiology

of OCD (26,27). In support of this hypothesis, addition of low dose neuroleptic to fluvoxamine treatment augmented the therapeutic response in treatment-refractory patients (40,60). The finding that the repetitive, seemingly uncontrollable motor behaviors observed here are dependent on 5-HT–DA interactions would corroborate this notion. In view of suggestions that compulsive motor behaviors in animals may model certain aspects of OCD (30,48), further characterization of 5-HT mediated oral stereotypy may contribute to our understanding of this complex disorder.

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