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Role of Dopamine in Behavioral Effects of Serotonin Microinjected into Rat Striatum

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YEGHIAYAN, S. K., A. E. KELLEY, N. S. KULA, A. CAMPBELL AND R. J. BALDESSARINI. *Role of dopamine in behavioral effects of serotonin microinjected into rat striatum.* PHARMACOL BIOCHEM BEHAV **56**(2) 251–259, 1997.—Bilateral local microinfusion of serotonin (5-hydroxytryptamine; 5-HT) into the ventrolateral striatum (VLS) of the rat forebrain induces quantifiable stereotyped orofacial behaviors. The role of presynaptic dopamine (DA) and structural requirements of indoles for expression of this behavioral effect and for inhibition of neuronal transport of [^{3}H]DA were examined. Bilateral local injection of 6-OHDA (8 μg/side) into VLS depleted DA and markedly diminished the behavioral effects of 5-HT. Intracerebral pretreatment with the potent DA transport inhibitors GBR-12909 (6 μg/side) or nomifensine (4 μg/side) also markedly decreased behavioral responses to 5-HT. A series of indoles and tyramine were examined for ability to induce stereotypy following infusion into the VLS. Of compounds tested, only *p*-tyramine, 5-HT, tryptamine and L-5-hydroxytryptophan (5-HTP) elicited strong orofacial behaviors; indoles lacking a free amino group or containing other substituents were virtually inactive in vivo, and the effect of 5-HTP was prevented by systemic pretreatment with the decarboxylase inhibitor NSD-1015, indicating its required conversion to 5-HT. Uptake of [^{3}H]DA (0.1 μM) into rat striatal synaptosomes was inhibited in a concentration-dependent manner in the following apparent rank-order: *p*-tyramine, *N*-methyl-5-HT, tryptamine, 5-HT, *N*-methyltryptamine (IC_{50} = 44-718 nM), other indoles (IC_{50} = 10-100 μM). These results support the conclusion that oral stereotypy induced by microinjection of 5-HT or other aromatic amines into rat VLS is mediated by local release of endogenous DA. These results extend previous findings indicating that this effect of 5-HT was not blocked by 5-HT receptor antagonists, and suggest mediation by a neuronal transport process involved in the uptake or storage of DA. **Copyright © 1997 Elsevier Science Inc.**

Behavior Dopamine 5-hydroxytryptamine Indoleamines Serotonin Stereotypy Striatum Transport Tyramine Uptake

SEROTONIN (5-hydroxytryptamine; 5-HT) can modulate effects of dopamine (DA) in mammalian forebrain, but the interactions are complex and not fully understood. Findings of both enhanced and decreased DA release associated with increased availability of 5-HT have been reported (1,4,6, 8,16,21,25,30,66,67). Mechanisms underlying 5-HT-induced release of DA, in particular, are not clear. 5-HT might release DA from its terminals by passive bulk displacement from intracellular pools, by competing for active transport, or by 5-HT receptor-mediated mechanisms. Jacocks and Cox (34) showed that 5-HT can release [^{3}H]DA from superfused rat striatal minces. Efflux of DA was blocked in these experiments by the relatively selective DA transport inhibitors GBR-12909, nomifensine and cocaine, while selective and non-selective antagonists for 5-HT_1, 5-HT_2 and 5-HT_3 receptors had no effect. With the same technique, other investigators (6,46) also found enhanced release of [^{3}H]DA from rat striatal slices following addition of 5-HT to a superfusion buffer. Again, the DA-releasing effect of 5-HT was not blocked by the non-selective 5-HT antagonist methysergide, but was blocked by the DA uptake inhibitors nomifensine and benztropine (46). These findings suggest that 5-HT can induce DA release in rat striatum by a non-receptor-mediated mechanism, perhaps involving inhibition or reversal of the DA uptake process mediated by its neuronal or vesicular membrane transporters.

Serotonin and agonists selective for particular 5-HT recep-

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tors also can induce stereotyped behaviors in the rat (13, 19,31,42). These may be mediated by direct stimulation of 5-HT receptors, or indirectly through dopaminergic activation. Complex interactions between 5-HT and DA with respect to stereotyped responses and other behaviors characteristic of extrapyramidal motor function have been described (3,14, 15,23,54,65,71). For example, Donohoe and colleagues (23) demonstrated an inhibition of stereotyped components of a 5-HT behavioral syndrome in rats following subcutaneous administration of LY-165,163, a piperazine compound that has both 5-HT_{1A} agonist and DA antagonist properties (29). Systemic administration of the tetralin 8-hydroxy-*N,N*-di-*n*-propylaminotetrahydronaphthalene (8-OH-DPAT), a 5-HT_{1A} agonist believed to lack effects at DA receptors, induced stereotyped behaviors in the rat (63). In addition, others (64) recently reported that 8-OH-DPAT reversed catalepsy induced in the rat by the DA D_2/D_3 antagonist raclopride, suggesting a functional interaction between 5-HT_{1A} receptors and dopaminergic motor functions mediated by D_2 or D_3 receptors in the extrapyramidal motor system of mammalian brain. It has also been reported that a synergistic interaction between striatal 5-HT and DA may act to modulate cocaine-induced changes in expression of transcription factor genes in brain tissue (11).

We recently found that infusion of 5-HT into the ventrolateral striatum (VLS) of rat brain produces a syndrome of stereotyped licking, biting and gnawing (68,69) that is strikingly similar to effects of locally injected DA agonists (37,38). This region of striatum is critically involved in the modulation of orofacial behavior (36–38,51). Non-selective 5-HT antagonists, as well as those selective for 5-HT receptor types 1, 2 or 3, did not affect expression of the behaviors induced by 5-HT placed in the VLS, while DA D_1 and D_2 antagonists markedly reduced the orofacial stereotypy, suggesting mediation by DA through mechanisms not associated with 5-HT receptors (69). These findings thus implicated an indirect action of 5-HT on DA in the VLS region.

The present experiments further examined the role of presynaptic DA in the stereotyped behavioral effect of local microinjections of 5-HT into the rat VLS. One experiment locally depleted DA in VLS by lesioning its nerve terminals with the toxin, 6-hydroxydopamine (6-OHDA) to test further for the contributions of DA and possibly 5-HT-receptive DA neurons as contributors to the actions of 5-HT. In addition, the role of DA transport processes in mediating possible presynaptic effects of 5-HT on DA terminals was assessed with the potent and selective DA transport inhibitors GBR-12909 and nomifensine. The molecular specificity of the behavioral effect of 5-HT was tested by comparing its behavioral efficacy with that of a series of indoles and the potent catecholamine releasing agent tyramine. Finally, the resulting structure-activity series was compared with the potency of the same compounds to inhibit [^{3}H]DA transport into striatal synaptosomes.

METHODS AND MATERIALS

Animals and Surgery

A total of 105 adult male, Sprague–Dawley albino rats (Charles River Breeding Laboratories, Wilmington, MA) weighing approximately 300 g (*ca.* 60 days old) were housed individually in clear plastic cages with free access to food and water and kept on a 12 h light/dark cycle (lights on 07:00-19:00 h). Before behavioral experimentation, rats were habituated to handling to minimize stress during testing.

In all experiments, rats were implanted with bilateral stainless steel guide cannulae (23 ga., 0.64 mm OD, 0.33 mm ID) aimed above the VLS under anesthesia with sodium pentobarbital (60 mg/kg, IP). The guide tips were implanted 2.5 mm above (D-V −4.7 mm) the VLS injection target located at coordinates: A-P + 1.8 mm from bregma, L-M ± 4.0 mm from midline, and D-V–7.2 mm from the skull surface, based on the rat brain atlas of Pellegrino and Cushman (48). Guides were affixed to the skull with dental acrylic and wire stylets were placed in the guide cannulae to prevent occlusion.

DA was depleted in the VLS by bilateral injection of 6-OHDA (8 μg/2 μl in physiologic saline containing 0.5 mM ascorbic acid). The neurotoxin was delivered over 8 min, and an additional 4 min was allowed for local diffusion as described below. Control animals received the vehicle at the same vol and rate. These animals were pretreated with the monoamine oxidase (MAO) inhibitor pargyline hydrochloride (50 mg/kg, IP) 30 min prior to infusion of the neurotoxin. Guide cannulae were implanted immediately after the administration of 6-OHDA in the neurotoxin-lesioned animals and their controls. Behavioral testing began 7–9 days after 6-OHDA treatment to allow time for degeneration of DA neurons, but at 2 days following implantation of guide cannulae in other groups.

Microinfusion Procedure

Prior to first testing, all animals received a preliminary infusion of vehicle into the VLS to adapt them to the microinjection procedure. Intracerebral injections of 150 mM saline or distilled water were used as matched vehicle controls for drug injections. For infusion, bilateral stainless steel injector cannulae (30 ga.) attached by polyethylene tubing (PE-10) to 10 μl Hamilton syringes were lowered through the guide to the injection target site in VLS. Intracerebral injections were delivered simultaneously in 0.5 μl or 1 μl/side over 2.5 min with a microdrive infusion pump (Harvard Apparatus, So. Natick, MA) as described below. Following an additional min to permit diffusion, injection cannulae were removed and guide stylets were replaced. In all experiments, pargyline (25 mg/kg, IP) was administered 30 min prior to microinfusion to prevent rapid degradation of injected amines. A repeated measures design was used; different treatments or drug doses were administered in a counterbalanced order across test days with 1–4 days of rest between drug treatments.

Behavioral Testing

Immediately following intra-VLS infusion, rats were returned to their home cages for behavioral scoring. A trained observer, kept blind to treatment, recorded behavior in 18 one-min observation periods, every five min, over 90-min test sessions. Oral behaviors were defined as follows: *lick*, licking any part of cage; *bite*, biting any part of cage; *self-gnaw*, gnawing any part of body; *mouth movements*, spontaneous mouth movements not directed toward cage or body; *taffy-pull*, repetitive paw-to-mouth movements; *head-down sniff/paw*, repetitive snout and paw movements directed down through floor grid in cage. Other behaviors recorded included *still*, either sleeping or motionless for entire observation period; *loco*, entire body crossing center line of cage; *rear*, rearing up on hind leg; and *groom*, grooming any part of body. Behaviors were scored as present (1) or absent (0) during each 1-min period. A combined score termed orofacial stereotypy was obtained by summing individual scores for the five categories of *lick, bite, self-gnaw, taffy-pull* and *head-down sniff/paw*.

Since individual animals expressed different behaviors at different times, the combined score proved to be a reliable indicator of drug-induced stereotypy. A total score for each category over the entire 90-min session was obtained as the sum of 1-min scores.

Synaptosomal Uptake of Dopamine

An isolated nerve terminal (synaptosomal) fraction of corpus striatum tissue was prepared after rapidly removing whole brains from decapitated rats. Brains were rinsed in ice-cold isotonic sucrose (0.32 M) and bilateral corpora striata were dissected on ice, weighed (80-100 mg), homogenized manually in ca. 120 vols of the sucrose in a Kontes Teflon-on-glass homogenizer and centrifuged for 10 min at 900 × *g* at 4°C (Beckman J-6B centrifuge, Irvine, CA). The first supernatant (S1) was recentrifuged (Sorvall RC-5B centrifuge, DuPont, Wilmington, DE) for 20 min at 15,000 × *g* to obtain a P2 pellet. This was suspended in 35 vols of original tissue weight in a modified, slightly hypertonic (58) physiological buffer (pH = 7.0) containing (mM): NaCl (124.0), KCl (5.0), KH_2PO_4 (1.4), $MgCl_2.6H_20$ (1.3), $CaCl_2.2H_20$ (0.8), HEPES (200.0), Na ascorbate (15.0), glucose (9.9), sucrose (80.0) and pargyline (0.015). The final striatal P2 synaptosome-rich homogenate (50 μl, *ca.* 1.4 mg of original tissue) was added to glass tubes containing assay buffer and test drug and preincubated for 3 min, after which 50 μl of [^{3}H]DA/DA was added to yield a final assay vol of 0.5 ml. Radioactively labeled [7-^{3}H]DA ([^{3}H]DA; 20 Ci/mmol, DuPont-NEN, Boston, MA) was diluted with fresh unlabeled DA (Sigma Chemical Co., St. Louis, MO) in ice-cold assay buffer to provide a final assay concentration of 0.1 μM. Tubes were incubated at 37°C for 10 min with 3 replicates per condition. Blank assay tubes contained excess DA transport inhibitor GBR-12909 (10 μM) and were incubated on ice. The synaptosomal uptake reaction was stopped by placing assay tubes in an ice bath. Assay mixtures were then filtered through cellulose ester microfilters (0.8 μM pore size, Micron Separations, Inc., Westboro, MA) on Millipore manifolds (Waters Assoc., Milford, MA). Tubes were washed twice (1 ml each) with ice-cold saline and filters were rinsed three times (3 ml each) with ice-cold saline, then counted for tritium in a liquid scintillation counter (efficiency ca. 50%; LKB-Wallac, Gaithersburg, MD). Data were analyzed by subtracting a corresponding blank (average = 12% of total counts of [^{3}H]DA in control assays) for each condition and computing inhibition of [^{3}H]DA transport as a percent of untreated control values (100%), which averaged 103 ± 11.4 fmol [^{3}H]DA taken up per mg of P2 protein per 10 min assay.

Drugs

The following compounds were purchased from Research Biochemicals Intl. (RBI, Natick, MA): 1-[2-[*bis*(4-fluorophenyl)methoxy]ethyl]-4-[3-phenylpropyl]piperazine dihydrochloride (GBR-12909), 2-methyl-5-hydroxytryptamine maleate (2-methyl-5-HT), 5-hydroxyindoleacetic acid (5-HIAA), 5-hydroxytryptamine hydrochloride (5-HT), 5-methoxy-*N,N*-dimethyltryptamine oxalate, 5-methoxytryptamine hydrochloride, 6-hydroxydopamine hydrobromide (6-OHDA), tryptamine hydrochloride, and *p*-tyramine hydrochloride. In addition, 3-hydroxybenzylhydrazine (NSD-1015), 5-hydroxyindole, L-5-hydroxytryptophan (5-HTP), *N*-methyltryptamine, L-tryptophan, dopamine, and pargyline hydrochloride were purchased from Sigma Chemical Co. (St. Louis, MO); 5-hydroxytryptophol, *N*,α-dimethyltryptamine, and *N*-methyl-5-hydroxytryptamine (*N*-methyl-5-HT) were obtained from Regis Chemical Co. (Chicago, IL). Nomifensine maleate was donated by Hoechst-Roussel Pharmaceuticals, Inc. (Somerville, NJ). 5-HT was dissolved in 150 mM sodium chloride. *N*-methyltryptamine and *N*,α-dimethyltryptamine were dissolved in 1:1 (vols) dimethylsulfoxide (DMSO):distilled water. Nomifensine was dissolved in β-cyclodextrin (45%, w/v, in distilled water). All other drugs used in behavioral studies were dissolved in distilled water. Stock solutions of all compounds used in uptake studies were dissolved in 1:1 (vols) ethanol:distilled water.

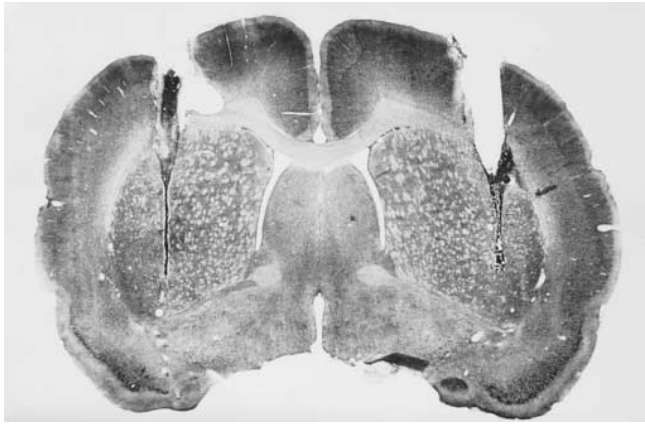


FIG. 1. Photomicrograph from representative animal depicting bilateral placements of guide and injector cannulae in rat ventrolateral striatum (VLS).

Histological and Biochemical Analyses

Infusion sites were verified by postmortem histological analysis of cannula tracks. With the exception of the 6-OHDA-treated rats, at the end of behavioral testing, all animals were deeply anesthetized with sodium pentobarbital (60 mg/kg, IP) and perfused transcardially with isotonic saline (150 mM) followed by 10% formalin (4% formaldehyde, w/v). Brains were removed and sectioned with a Lancer Vibratome (Technical Products Intl., St. Louis, MO). Cresyl-violet stained sections were examined by light microscopy and the location of cannula tracks and their tips (estimated site of injection) were recorded. Photomicrographs of cannula placements in rat VLS were made from representative sections (see Fig. 1).

Animals in the 6-OHDA study were sacrificed and their brains dissected for verification of tissue DA concentrations by high-pressure liquid chromatography (HPLC) according to the methods of Cousins and Salamone (18). Brains were frozen quickly and 1.0-mm thick coronal sections were cut. A hollow stainless steel tube (16 ga.) was used to punch out sections of tissue in the VLS (ca. 11 mg). Tissue samples were disrupted by sonication in ice-cold 0.1 N perchloric acid and centrifuged (10,000 × *g* for 4 min). The supernatant was assayed for DA by HPLC, using a dual-piston pump (Waters Assoc., Milford MA), a precolumn filter, a reverse-phase column, a Coulochem electrochemical detector, and a chart recorder. The mobile phase was 200 mM phosphate buffer (pH 4.5) with 7.0% (vols) methanol, 2.8 ml of 0.4 M sodium octyl sulphate, and 0.75 ml of 100 mM EDTA. Analytical standards of DA were assayed before, during and after the tissue samples. Resulting DA concentrations are expressed as ng/mg wet VLS tissue.

Statistical Analysis

Data were analyzed using either one- or two-tailed Student's t-test or two-factor analysis of variance with repeated measures where appropriate. Further analyses were conducted using planned contrasts between means in drug conditions vs. lesion, pretreatment, or time (50). Potency data were analyzed with the ALLFIT curve-fitting program adapted for the Macintosh microcomputer (22, 62) to determine ED_{50} or $IC_{50} \pm SE$.

Experimental Design

Experiment I: Effect of 6-OHDA lesion of VLS on 5-HT-induced stereotypy. The ability of a range of doses of 5-HT to elicit orofacial stereotypy was examined in 6-OHDA-lesioned ($n = 10$) and control ($n = 7$) rats. At 7-9 d after 6-OHDA lesioning, rats received bilateral VLS infusions of vehicle (VEH) or 5-HT (0, 0.2, 2, 10, 20 μg/1.0 μl) in counterbalanced order, and behavior was observed for 90 min and scored as described above.

Experiment II: Effect of DA transport inhibition on 5-HT-induced stereotypy. The effects of pretreatment with the selective DA transport inhibitors GBR-12909 or nomifensine were investigated. GBR-12909 (6 μg/1.0 μl) or its vehicle was microinjected bilaterally into the VLS in a counterbalanced order across four test days in 15 rats ($n = 8$ GBR; $n = 7$ VEH), followed 5 min later by 5-HT (0, 2, 10, 20 μg/0.5 μl). Additional rats ($n = 6$) were microinfused with nomifensine (4 μg/1.0 μl) or vehicle followed 20 min later by 5-HT (10 μg/0.5 μl) into the VLS. 5-HT was infused in 0.5 rather than 1 μl to minimize tissue damage. Behavior was scored for 90 min.

Experiment III: Structural requirements for indoles to elicit stereotypy Five groups of rats was given 2-7 injections with various indoles, tyramine, or saline bilaterally into the VLS. Each series of injections (1 μl/side) were given in a counterbalanced order separated by at least two days. The first group ($n = 7$) was given L-tryptophan (10 μg), 5-hydroxytryptophol (10 μg), *N*,methyltryptamine (20 μg), *N*,α-dimethyltryptamine (20 μg), 5-HT (20 μg), tryptamine (20 μg), and the catecholamine-releasing agent, *p*-tyramine (20 μg), for a total of seven injections. A second group ($n = 5$) was given *N*-methyl-5-hydroxytryptamine (20 μg), 5-hydroxyindole (20 μg), and 5-methoxytryptamine (20 μg), for a total of three injections. A third ($n = 8$) was given 2-methyl-5-hydroxytryptamine (15 μg) and saline. A fourth ($n = 7$) was given L-5-hydroxytryptophan (5-HTP, 20 μg), 5-hydroxyindoleacetic acid (20 μg) and saline. A fifth ($n = 5$) was given 5-methoxy-*N,N*-dimethyltryptamine (20 μg) and saline. Doses were chosen to be approximately equimolar to doses of 5-HT (10-20 μg) that were 2.5-5.0 times above its previously determined and reverified ED_{50} (69).

To test whether behavioral effects of 5-HTP (20 μg) required conversion to 5-HT, some rats ($n = 7$) were pretreated with a centrally active dose of the aromatic amino acid decarboxylase inhibitor NSD-1015 (100 mg/kg, IP) 40 min prior to infusion of 5-HTP into VLS, and behavior was recorded for 90 min.

Experiment IV: Structural requirements for indoles to inhibit [^{3}H]DA uptake by striatal synaptosomes. The following compounds were examined in a range of concentrations (1 nM-100 μM) for ability to inhibit accumulation of [^{3}H]DA by striatal synaptosomes: 5-HT, *p*tyramine, tryptamine, 5-HTP, *N*-methyl-5-HT, *N*-methyltryptamine, 5-methoxytryptamine, 5-methoxy-*N,N*-dimethyltryptamine, 2-methyl-5-HT, *N*,α-dimethyltryptamine, 5-hydroxyindoleacetic acid, and L-tryptophan.

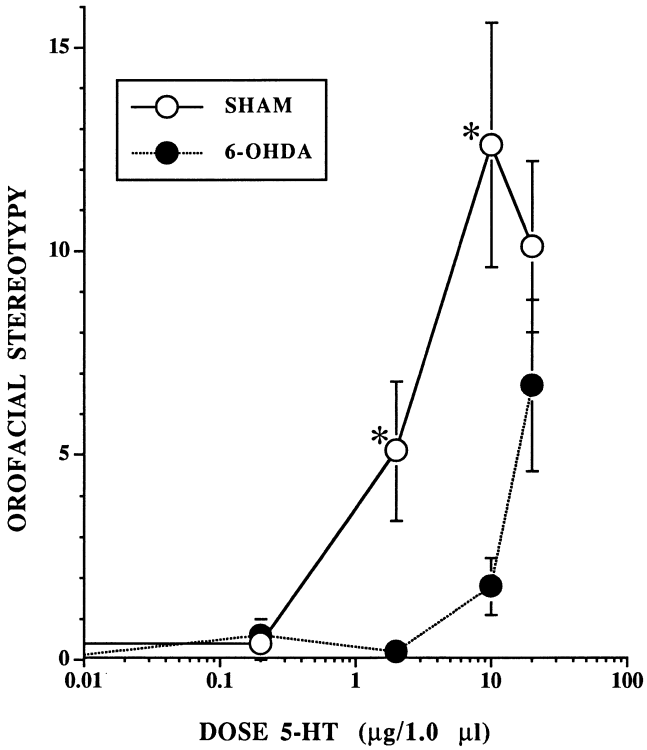


FIG. 2. Effect of 6-OHDA treatment on stereotypy induced by infusion of 5-HT (0, 0.2, 2, 10, 20 μg/1.0 μl/side) into ventrolateral striatum (VLS). Values represent mean scores ± SEM ($n = 17$); (*) $p < 0.01$.

RESULTS

I. Behavioral Effects of 5-HT Infusion into VLS Following DA Depletion

As we found previously (69), infusion of 5-HT into the rat VLS induced orofacial stereotypy in a dose-dependent manner ($ED_{50} = 3.9 \pm 0.8$ μg/side; Fig. 2). Sham-treated animals challenged with intra-VLS doses of 5-HT of 2 μg/side showed strong, repetitive orofacial behaviors primarily characterized by self-gnawing and intense sniffing and pawing of cage floor. 6-OHDA pretreated rats showed an 84.2% depletion of DA in tissue from the VLS target area (from 4.0 ± 0.3 to 0.6 ± 0.2 ng/mg; t [15 df] = 10.5, one-tailed $p < 0.0001$). Lesioned rats appeared physically and behaviorally normal. Mean postoperative body weight of 6-OHDA-treated rats was not significantly different from sham-treated animals (lesion vs. sham; 299 ± 11 vs. 319 ± 6 g; t [15 df] = 1.44, one-tailed $p > 0.05$). Depletion of DA in VLS with 6-OHDA markedly reduced the behavioral response to 5-HT. Two-factor ANOVA indicated a significant main effect for dose [$F(4, 58) = 16.1$, $p < 0.001$] and for treatment [lesion vs. sham; $F(1, 15) = 17.2$, $p < 0.001$], as well as a significant interaction between dose and treatment [$F(4,58) = 5.5$, $p < 0.001$]. Contrast analysis indicated that drug-control differences at the 2 and 10 μg doses were highly significant ($p < 0.01$ and $p < 0.0001$, respectively). The potency of 5-HT was markedly reduced one week after local 6-OHDA lesioning, since the computed $ED_{50} \pm SE$ was 8.7-times lower in control vs. lesioned rats (2.2 ± 0.5 vs. 19.2 ± 0.6 μg/side; t [8 df] = 20.8, two-tailed $p < 0.001$).

II. Effects of pretreatment with GBR-12909 or nomifensine on 5-HT-induced orofacial stereotypy. Response to 5-HT was examined after intracerebral injection of GBR-12909 (6 μg/1.0 μl) or its control vehicle at 5 min before intra-VLS injection of a range of doses of 5-HT (0, 0.2, 2, 10, 20 μg/0.5 μl). There were significant main effects for GBR-12909 pretreatment [$F(1,13) = 10.4$, $p < 0.01$] and dose of 5-HT [$F(3,39) = 10.6$, $p < 0.0001$], with a trend toward a pretreatment-by-dose interaction. GBR-12909 pretreatment significantly inhibited the response to 10 and 20 μg/side doses of 5-HT [$F = 13.6$ and 9.4, respectively, $p < 0.01$ by contrast analysis; Fig. 3]. At the dose used (6 μg/side), GBR-12909 by itself had no measurable effect on stereotyped or other behaviors including locomotion, rearing and grooming (data not shown). Local nomifensine pretreatment also significantly inhibited stereotypy induced by 5-HT (10 μg/0.5 μl), from 9.2 ± 2.7 in controls to 1.2 ± 1.0 (t[11 df] = 2.1, one-tailed $p < 0.05$).

III. Ability of indoles to induce orofacial stereotypy. Among the indoles tested (see Table 1), only 5-HT (t [12 df] = 6.0, $p < 0.0001$), tryptamine (t [11 df] = 3.4, $p < 0.01$) and L-5-hydroxytryptophan (5-HTP; t [12 df] = 6.2, $p < 0.0001$) elicited strong orofacial behavioral responses; the catecholamine-releasing agent *p*-tyramine also elicited very strong stereotypy (t [11 df] = 11.4, two-tailed $p < 0.0001$; Table 2). The behavioral effect of 5-HTP was blocked by pretreatment with the centrally active decarboxylase inhibitor, NSD-1015 (77.5% inhibition; t [13 df] = 3.4, $p < 0.01$), suggesting that the behavioral activity of this compound required conversion to 5-HT. All other compounds tested were inactive or elicited very low levels of stereotypy (all scores 1.6, compared to 0.4 ± 0.3 for vehicle controls; Table 2).

IV. Ability of indoles to compete for [^{3}H]DA transport into striatal synaptosomes. High in vitro potency vs. uptake of [^{3}H]DA (0.1 μM) into striatal synaptosomes was found with the following compounds (IC_{50} ± SE, μM): *p*-tyramine (0.04 ± 0.03), *N*-methyl-5-HT (0.11 ± 0.12), tryptamine (0.42 ± 0.13), 5-HT (0.71 ± 0.28), *N*-methyltryptamine (0.72 ± 0.28). Other

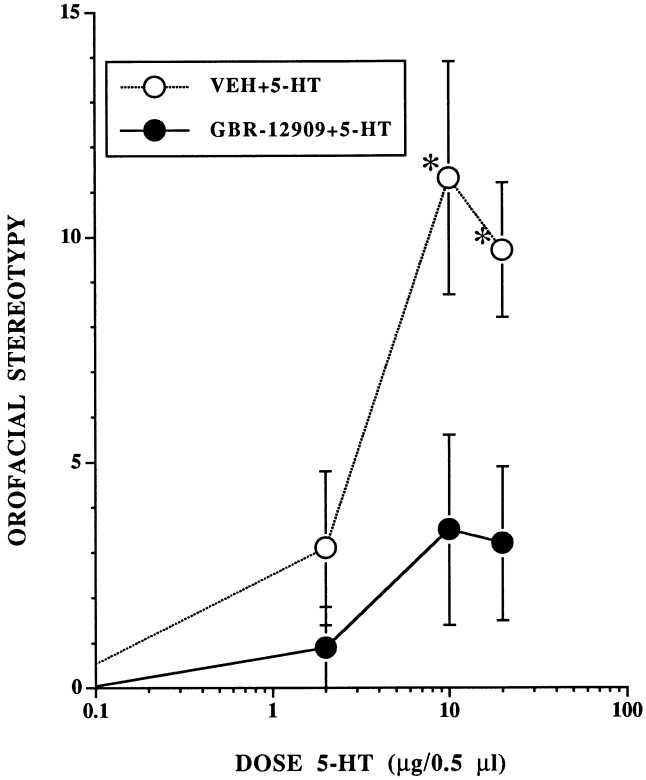
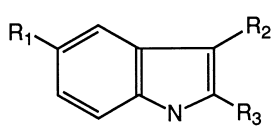


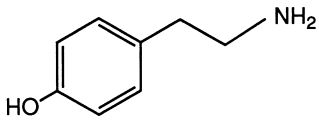
FIG. 3. Dose-response relationship of 5-HT (0, 2, 10, 20 μg/0.5μl/side) microinjected into VLS following GBR-12909 (6 μg/1.0 μl) pretreatment. Values represent mean scores ± SEM ($n = 15$; dose 5-HT (10 μg) $n = 22$); (*) $p < 0.01$.

TABLE 1

STRUCTURES OF INDOLES AND *p*-TYRAMINE TESTED *IN VIVO* AND *IN VITRO*



Indoles



***p*-Tyramine**

Compound	R_1	R_2	R_3
p-Tyramine	—	—	—
5-Hydroxytryptamine (5-HT)	OH	$CH_2CH_2NH_2$	H
Tryptamine	H	$CH_2CH_2NH_2$	H
N-Methyl-5-hydroxytryptamine	OH	$CH_2CH_2NHCH_3$	H
5-Methoxytryptamine	OCH_3	$CH_2CH_2NH_2$	H
5-Methoxy-*N,N*-dimethyltryptamine	OCH_3	$CH_2CH_2N(CH_3)_2$	H
N-Methyltryptamine	H	$CH_2CH_2NHCH_3$	H
2-Methyl-5-hydroxytryptamine	OH	$CH_2CH_2NH_2$	CH_3
N,α-Dimethyltryptamine	H	$CH_2CH(CH_3)NHCH_3$	H
L-5-Hydroxytryptophan (5-HTP)	OH	$CH_2CH(COOH)NH_2$	H
L-Tryptophan	H	$CH_2CH(COOH)NH_2$	H
5-Hydroxytryptophol	OH	CH_2CH_2OH	H
5-Hydroxyindoleacetic acid	OH	CH_2COOH	H
5-Hydroxyindole	OH	H	H

TABLE 2

EFFECTS OF INDOLES AND *p*-TYRAMINE ON ORAL STEREOTYPY IN RAT AFTER INFUSION INTO VENTROLATERAL STRIATUM

Compound	Stereotypy
p-Tyramine	21.0 ± 1.9*
L-5-Hydroxytryptophan (5-HTP)	17.1 ± 2.7*
5-Hydroxytryptamine (5-HT)	11.0 ± 1.7*
Tryptamine	9.2 ± 2.8*
N-Methyl-5-hydroxytryptamine	1.6 ± 1.1
5-Methoxy-*N,N*-dimethyltryptamine	1.4 ± 1.4
5-Methoxytryptamine	1.0 ± 0.8
L-Tryptophan	0.4 ± 0.4
5-Hydroxytryptophol	0.4 ± 0.3
5-Hydroxyindoleacetic acid	0.3 ± 0.3
N-Methyltryptamine	0.3 ± 0.3
2-Methyl-5-hydroxytryptamine	0.0 ± 0.0
N,α-Dimethyltryptamine	0.0 ± 0.0
5-Hydroxyindole	0.0 ± 0.0
Saline	0.4 ± 0.3

Scores are means ± SEM (90 min); *$p < 0.01$.

Dose of test agents are all approximately equimolar to a highly effective dose of 5-HT (20 μg/side or 0.1 μmol/side) shown to produce a robust stereotypy response.

indoles were much less potent ($IC_{50} > 10$ μM), including: 5-methoxytryptamine, 5-methoxy-*N,N*-dimethyltryptamine, 2-methyl-5-HT, *N*-α-dimethyltryptamine, 5-hydroxyindoleacetic acid, 5-HTP, L-tryptophan (Table 3).

DISCUSSION

The present results extend our previous findings indicating an essential role of presynaptic DA in the orofacial stereotypy that follows microinjection of 5-HT into rat VLS. Pretreatment with locally injected 6-OHDA to deplete endogenous DA in the VLS markedly inhibited 5-HT-elicited stereotypy at intermediate doses of the indoleamine, whereas a supramaximal dose of 5-HT (20 μg/side) may have been sufficient to "activate" residual DA, and stereotypy at this dose of 5-HT was not significantly inhibited by 6-OHDA pretreatment (Fig. 2). The inhibitory effect of 6-OHDA on stereotypy induced by intermediate doses of 5-HT (2 and 10 μg/side) complements our earlier finding (68,69) that removal of endogenous DA with reserpine and α-methyl-*p*-tyrosine also prevented the behavioral response to 5-HT. Dependency of the effect of 5-HT on endogenous DA is further supported by the previously reported ability of the D_1 DA antagonist SCH-23390 and the D_2/D_3 DA antagonist raclopride to abolish the stereotyped behavior produced by 5-HT, while various selective (for 5-HT receptor types 1, 2, or 3) and broad-spectrum 5-HT antagonists had little or no effect (68,69). Instead, the present findings of decreased 5-HT-induced stereotypy following intra-VLS DA depletion and local GBR-12909 or nomifensine pretreatment implicates endogenous DA in mediating the effect of locally injected 5-HT, and suggests involvement of DA transport processes.

Mechanisms by which 5-HT may influence the storage, metabolism, and release of DA remain unclear and may be complex. Some studies have implicated specific 5-HT receptor types in facilitating striatal dopaminergic activity. For example, findings from *in vivo* microdialysis studies and other metabolic measures of activity in DA pathways (including the rate of accumulation of the DA metabolite 3-methoxytyramine in vivo following pretreatment with an MAO inhibitor) have implicated 5-HT_1 receptors (subtype 1B in particular) in facilitating release of DA from the rat striatum and nucleus accumbens (8,30,45,47,67). Additionally, some evidence supporting a role of 5-HT_4 receptors in releasing DA has recently been reported (9,57,59), but this proposed effect requires further evaluation with more selective compounds. Regarding the present study, the indole 5-methoxytryptamine, considered a potent, but non-selective 5-HT_4 agonist (24,56), produced only weak stereotypy (see Table 2). Use of more selective 5-HT_4 compounds with long lasting *in vivo* effects may allow further examination of a role for this serotonin receptor type in the 5-HT-induced orofacial stereotypy that appears to be mediated via DA release. Furthermore, using superfused rat striatal slices *in vitro*, Blandina and colleagues (12) reported that 5-HT, as well as the 5-HT_3 agonist 2-methyl-5-HT, increased [^{3}H]DA efflux, and that its effect was blocked by the partial 5-HT_3 antagonist ICS-205-930, whereas 2-methyl-5-HT was inactive in the present test systems (Tables 2 & 3).

Other findings (10,17,35,53) also support a role of 5-HT_3 agonists in the release of DA from the striatum and nucleus accumbens, but indicate that non-receptor-mediated actions may contribute to the effects of some of these agents. In particular, the 5-HT_3 agonist 1-phenylbiguanide (1-PBG) released [^{3}H]DA from superfused rat striatal slices (10,53). However, its DA-releasing effects were not blocked by 5-HT_3 antagonists ICS-205-930, MDL-73,147, or zacopride, and were insensitive to calcium in the superfusion medium, but were markedly inhibited by the DA transport blocker nomifensine. Similarly, Yi and colleagues (70) found that [^{3}H]DA efflux from striatal synaptosomes was induced by 5-HT and blocked by the DA transport inhibitors cocaine and nomifensine, but not by the 5-HT_3 receptor antagonists MDL-72222 or GR-38032F. We previously reported no behavioral effect of the 5-HT_3 agonists 1-PBG or 2-methyl-5-HT following microinjection into rat VLS, nor an inhibitory effect of MDL-72222 and GR-38032F on behaviors induced by local administration of 5-HT (69).

It may be that 5-HT interacts with DA neurons by competing for transporters for DA in cell membranes or synaptic vesicles since these transport processes regulate the neuronal

TABLE 3

IN VITRO POTENCY OF INDOLES AND TYRAMINE VS. DOPAMINE UPTAKE BY RAT STRIATAL SYNAPTOSOMES

Compound	IC_{50} ± SE (μM)
p-Tyramine	0.044 ± 0.032
N-Methyl-5-hydroxytryptamine	0.110 ± 0.120
Tryptamine	0.415 ± 0.134
5-Hydroxytryptamine (5-HT)	0.708 ± 0.281
N-Methyltryptamine	0.718 ± 0.275
5-Methoxytryptamine	ca. 10.0
5-Methoxy-*N,N*-dimethyltryptamine	ca. 10.0
2-Methyl-5-hydroxytryptamine	ca. 50.0
N,α-Dimethyltryptamine	ca. 100
5-Hydroxyindoleacetic acid	ca. 100
L-5-Hydroxytryptophan	ca. 100
L-Tryptophan	ca. 100

and intraneuronal disposition of the catecholamine (39,52). Bidirectional active transport of DA out of, as well as into, cells has been demonstrated in rat striatum using a variety of DA-releasing agents and transport inhibitors (2,27,33,41,49). Specifically, 5-HT can induce DA efflux via a cell membrane transporter-dependent mechanism functionally linked to the sodium ion gradient (10,34,46,70). Carrier-mediated transport of DA is sodium-dependent, and reversal of the sodium gradient with ouabain or veratrine can both prevent uptake and induce efflux of DA in striatum (5,26). The mechanism of carrier-mediated efflux is believed to depend on a cytosolic pool of DA and not the vesicular pool involved in depolarization-induced, calcium-dependent exocytosis (2,32,40). Release of cytoplasmic DA by this non-exocytotic mechanism may occur in conditions of normal cytoplasmic DA concentrations, such that the cell transmembrane carrier protein is available on the intracellular surface and may act in reverse to transport DA out of its nerve terminals. This process may be even more prominent under conditions of increased cytoplasmic DA concentration, which can occur in a variety of circumstances. For example, Sulzer and Rayport (60,61) found that amphetamine (and other weak lipophilic bases including 5-HT and other indoleamines) can decrease the intraneuronal vesicular transmembrane pH gradient necessary for vesicular storage of DA, with a resultant shift in distribution of DA from vesicles to cytoplasm. Cytoplasmic DA increased in this manner may be a substrate for reverse cell membrane transport (*i.e.*, transport out of the cell), as is suggested by the ability of the transport blocker nomifensine to decrease release of endogenous DA induced by weak bases from cultured ventral midbrain neurons (61).

More generally, 5-HT might produce DA-mediated behavioral effects by enhancing neuronal release of DA through several possible mechanisms. These include: [i] altering the critical pH gradient across the membranes of DA storage vesicles, [ii] directly displacing vesicular stores of DA into cytoplasm, or [iii] enhancing carrier-mediated transport across the cell membrane (reverse uptake) (1,28,60,61). While complementary and not mutually exclusive, which of these alternatives is involved or predominant remains to be determined.

Induction of stereotyped behavior by indoles was chemically selective (Tables 1 & 2). The presence of a free amino group, as well as a free 5-hydroxyl group, led to the strongest stereotypy induced by indoleamines. This finding generally accorded with structural requirements for competition for neuronal transport of DA which appeared to favor compounds with a free amino group and an aromatic ring-hydroxy moiety (5,43; Table 3). Removal or occlusion of the 5-hydroxyl group of indoleamines slightly reduced the behavioral response, and absence of a free amino moiety from indoles markedly reduced stereotypy, even at a relatively high test dose at the molar-equivalent of 5-times ED_{50} for 5-HT itself. Addition of methyl groups to the amino nitrogen or the ethylamino side-chain 2-carbon, or a methyl or carboxyl moiety to the α-carbon of the side-chain abolished the behavioral response, perhaps by reducing affinity for the DA transporter by steric or electrostatic interference with critical docking sites.

The present results from *in vitro* assessment of the competitive inhibition of [^{3}H]DA transport by indoles and tyramine suggest a similar, although not identical, molecular profile. The most potent inhibitors of [^{3}H]DA transport into striatal synaptosomes were *p*-tyramine, followed by *N*-methyl-5-HT, tryptamine, 5-HT and *N*-methyltryptamine, suggesting that removal of the 5-hydroxyl group or addition of a single methyl group to the amino nitrogen did not entirely prevent an interaction with the [^{3}H]DA transporter. Several compounds that produced stereotyped behavioral responses when placed in the VLS also were active in inhibiting [^{3}H]DA transport into striatal synaptosomes. An exception was the immediate precursor of 5-HT, the amino acid 5-HTP, which was very active *in vivo*, but had little effect on initial uptake of [^{3}H]DA *in vitro*. Since the central decarboxylase inhibitor NSD-1015 strongly inhibited the behavioral effects of 5-HTP, the precursor probably acts by conversion to 5-HT *in vivo* (44). In the synaptosomal preparations, the level of decarboxylase activity and time of exposure may have been insufficient to permit substantial conversion of 5-HTP to 5-HT, and the tissue preparation used may favor intrasynaptosomal retention of newly formed 5-HT.

The results of the present experiments extend support for the thesis that some behavioral effects induced by 5-HT are mediated by release of endogenous DA from afferent DA terminals which richly innervate the striatum (7,20,55). Reversal of the DA transport process to facilitate transporter-mediated release of cytoplasmic DA, perhaps also facilitated by shifting of DA from vesicular to cytoplasmic pools, may contribute to the release of DA and to its mediation of 5-HT-induced stereotypy. This proposal is supported by the ability of the DA transport inhibitors GBR-12909 and nomifensine to prevent the behavioral action of 5-HT in the VLS, and by the molecular selectivity for hydroxylated aromatic monoamines to mimic the actions of 5-HT. In general, the behavioral effect observed after placing 5-HT in the rat VLS evidently is not mediated by 5-HT receptors and appears to require release of endogenous DA.

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