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Modulation of Oral Movements by Intranigral 5-Hydroxytryptamine Receptor Agonists in the Rat

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LIMINGA, U., A. E. JOHNSON, P. E. ANDRÉN AND L. M. GUNNE. *Modulation of oral movements by intranigral 5-hydroxytryptamine receptor agonists in the rat.* PHARMACOL BIOCHEM BEHAV 46(2) 427–433, 1993.—Bilateral infusion of 5-hydroxytryptamine (5-HT) agonists into the substantia nigra pars reticulata (SNr) of awake rats was shown to influence oral behavior. The 5-HT_{1A} agonist (*R*)-8-hydroxy-2-(di-propylamino)-tetralin (8-OH-DPAT) (1.3–13 nmol on each side) produced a dose-dependent depression of vacuous chewing movements (VCMs) that lasted about 20 min. The (*R*)-8-OH-DPAT-induced depression of VCMs was blocked by the simultaneous intranigral infusion of a specific 5-HT_{1A} antagonist [(−)-(*S*)-5-flouro-8-hydroxy-2-(dipropylamino)tetralin HCl (UH-301)], which had no effect when given alone. Another 5-HT_{1A} agonist [(5-methoxy-*N,N*-dimethyltryptamine hydrogen oxalate (5-MeO-DMT)] also reduced VCM frequencies. Intranigral infusion of the nonspecific 5-HT-agonists 1-(3-triflouro-methylphenyl) piperazine (TFMPP) and 1(*m*-chlorophenyl)-piperazine (mCPP) and a 5-HT_3 agonist [2-methyl-5-hydroxytryptamine (2-Me-5-HT)] increased VCM after 5- to 10-nmol doses. Another 5-HT_3 agonist (1-phenylbiguanide) and a 5-HT_2 agonist [1-(4-bromophenyl-2,5-dimethoxy)-2-aminopropane (DOB)] had no significant effect. As most 5-HT receptors in the SNr are of the 5-HT_{1B} subtype, these results suggest that the increased VCM frequency was mediated via nigral 5-HT_{1B} receptors. The importance of 5-HTergic mechanisms in the development of drug-induced dyskinesias is discussed.

5-HTergic drugs Intranigral infusion Substantia nigra Oral movements Dystonia Dyskinesia Rats

LONG-TERM exposure to compounds frequently used in the treatment of mental disorders such as schizophrenia are often associated with the development of extrapyramidal side effects like dystonia or dyskinesia (5). This class of drugs, known as neuroleptics, are potent blockers of dopamine (DA) transmission (7,35). In rats, long-term administration of neuroleptics produces a quantifiable oral behavior referred to as vacuous chewing movements (VCMs) that has been proposed as an animal model for drug-induced dyskinesias (15,42). In addition, recent clinical evidence has shown that compounds commonly used in the treatment of depression and anxiety that act by altering serotonergic [5-hydroxytryptamine (5-HT)] transmission may produce similar motor disturbances (4,43). A study of the influence of 5-HT compounds on oral behavior in rats provided early evidence that administration of 5-HT-selective drugs can increase the frequency of purposeless chewing and that 5-HT stimulated increases are mediated by 5-HT_{1B} receptors (38). However, because peripheral rather than central drug administration techniques were employed the results of this early study do not provide an indication of the site of action within the CNS of these 5-HT compounds. Further, it is possible that the reported differences in drug efficacy were related to the accessibility of the compounds to binding sites in the CNS either due to differences in permeability of the blood–brain barrier or drug metabolism.

One brain region that plays an important role in the development of tardive dyskinesia is the substantia nigra pars reticulata (SNr) (13). In rats, intranigral administration of compounds that affect GABAergic, enkephalinergic, and neurokinin transmitter systems have been found to alter DA transmission (18,33) and oral behaviors (14,25,26,34). Changes in 5-HT activity are also known to alter DA transmission in the substantia nigra (10,22). Further, 5-HT neurons located in the dorsal raphé project extensively to the substantia nigra (10,41), where a high density of 5-HT_1 receptors has been demonstrated (31). Interestingly, receptors in this brain region are predominantly of the 5-HT_{1B} subtype (31).

To examine the possible role of 5-HT transmission in the SNr on the development of movement disorders like dystonias or dyskinesias, the influence of bilateral intranigral infusions of 5-HT receptor agonists and an antagonist on oral movements in awake rats was investigated in the present experi-

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ments. The selective 5-HT_{1A} agonist (*R*)-8-hydroxy-2-(di-propylamino)-tetralin (8-OH-DPAT) (6) was studied alone and in combination with a specific 5-HT_{1A} antagonist (3). A number of less selective 5-HTergic compounds were also investigated.

METHODS

Animals

Female Sprague–Dawley rats weighing between 260 and 300 g (ALAB, Sollentuna, Sweden) were housed two per cage under standardized conditions (20–22°C, on a 12 L : 12 D cycle) with free access to commercial rat food and water.

Drugs

The following compounds were used in these studies: The highly selective, full 5-HT_{1A} agonist 8-OH-DPAT (6) and the selective 5-HT_{1A} antagonist (−)-(*S*)-5-flouro-8-hydroxy-2-(dipropylamino)tetralin HCl (UH-301) (3) were gifts from Dr. Uli Hacksell, Department of Organic Pharmaceutical Chemistry, Uppsala University. A less selective 5-HT_{1A} agonist [5-methoxy-*N,N*-dimethyltryptamine hydrogen oxalate (5-MeO-DMT)] (36), two nonselective 5-HT agonists [1-(3-triflouro-methylphenyl) piperazine (TFMPP) and 1(*m*-chlorophenyl)piperazine (mCPP)] (19,27), the 5-HT_2/5-HT_{1C} agonist 1-(4-bromophenyl-2,5-dimethoxy)-2-aminopropane (DOB) (39), and the 5-HT_3 agonists 2-methyl-5-hydroxytryptamine (2-Me-5-HT) (21) and *N*-phenyl-imidodicarbonimidic diamide (biguanide) (20) were purchased from Research Biochemicals Inc. (Natick, MA).

Intranigral Infusions

Surgery. Rats were anesthetized with an IP injection of Equithesin, 3.3 ml/kg, and placed in a stereotaxic instrument. Permanent 22-ga stainless steel guide cannulae were implanted bilaterally ending 2 mm above the infusion site and secured with dental cement. Stereotaxic coordinates for the infusion sites were: 3.2 mm caudal from bregma, 2.0 mm from midline, and 7.9 mm below dura, with the incisor bar placed 5.0 mm above the interaural line (32). After surgery, rats were given 2–5 days to recover.

Monitoring of oral behavior. Behavioral observations throughout the study were performed by an observer unaware of the different drug conditions. Premeasurement observations were done to screen rats before the start of the infusion. Implantation of guide cannulae can cause focal infections in the infusion area or other complications that may increase VCM frequencies above the normal range of 2–6 VCM/min (personal observation). Therefore, all rats with a VCM frequency higher than 6 VCM/min during any of the premeasurements were excluded from the study.

Rats were individually transferred to a plastic observation cage 40 × 25 × 15 cm equipped with mirrors and allowed to habituate for 2 min. Premeasurements of VCM were made at 9–11 and 4–6 min before the start of the infusion. The number of VCMs were counted at 0–1 min after the end of infusion and then for 2-min observational sessions at 4–6, 9–11, 14–16, 19–21, 24–26, 29–31, 39–41, 49–51, and 59–61 min postinfusion.

Drug infusions. Stainless steel internal cannulae (28 ga) were inserted immediately before the first VCM premeasurement. Over a 5-min period, 0.5 μl drug solution was simultaneously infused into each SNr. Drug delivery was accomplished with infusion pump-driven (Sage Instruments, Cambridge, MA) Hamilton syringes (10 μl) (Hamilton Co., Reno, NV) connected with polyethylene tubing to the infusion cannulae. The cannulae were left in place for 1 min postinfusion while the first VCM measurement was taken.

All drugs were dissolved in saline. The doses and volumes below refer to the amount of drug infused into each SNr: control treatment, infusion of 0.5 μl saline (n = 11); 8-OH-DPAT, 1.3 nmol (n = 7), 3.3 nmol (n = 6), 6.6 nmol (n = 5), or 13 nmol (n = 5); UH-301, 18 nmol (n = 6) or 40 nmol (n = 6); 8-OH-DPAT and UH-301, a solution of 8-OH-DPAT + UH-301 was given in the following dose combinations (8-OH-DPAT + UH-301)—1.3 nmol + 18 nmol (n = 7), 1.3 nmol + 40 nmol (n = 7), 3.3 nmol + 18 nmol (n = 7), 3.3 nmol + 40 nmol (n = 6); 5-MeO-DMT, 10 nmol (n = 8) or 20 nmol (n = 7); mCPP, 5 nmol (n = 6), 10 nmol (n = 6), or 20 nmol (n = 6); TFMPP, 5 nmol (n = 6), 10 nmol (n = 7), or 20 nmol (n = 7); DOB, 10 nmol (n = 5); 2-Me-5-HT, 10 nmol (n = 11) and 20 nmol (n = 8); biguanide, 10 nmol (n = 10) and 20 nmol (n = 6).

Histological Verification

To facilitate the verification of the placement of the cannula tips, 0.1–0.3 μl methylene blue (50 mg/ml in H_2O) was injected through the cannulae immediately after decapitation. The head was sliced in a cryomicrotome and the location of the cannulae was established by an observer unaware of the outcome of the behavioral measurements. Only rats with both cannulae tips in the SNr were included in the study.

Statistics

Eleven rats served as a saline-infused control group for all other drug conditions. The two VCM premeasurements were subjected to a two-way analysis of variance (ANOVA) (8) (drug group vs. time). The number of VCM/min for 0–30 min postinfusion were also subjected to a two-way ANOVA (8) (drug group vs. time) with repeated measurements on the time factor. Significant differences between groups or over time were subsequently analyzed with Tukey's posthoc test. All statistical analysis were run separately for each drug, including the saline-infused control group. The combinations of 8-OH-DPAT and UH-301 were analysed with separate ANOVAs. One comparison included the control group, 8-OH-DPAT 1.3 nmol, 8-OH-DPAT 1.3 nmol + UH-301 18 nmol, and 8-OH-DPAT 1.3 nmol + UH-301 40 nmol. The second consisted of control, 8-OH-DPAT 3.3 nmol, 8-OH-DPAT 3.3 nmol + UH-301 18 nmol, and 8-OH-DPAT 3.3 nmol + UH-301 40 nmol.

Linear regression analysis was performed to further examine the dose–response relationship between 8-OH-DPAT and VCM frequency. The area under the VCM/min curves from 0–20 min postinfusion (AUC 0–20 min) was calculated with the trapezoid rule $(t_2 - t_1) \times (y_1 + y_2)^{1/2}$ (12) and used as the response variable. The results of all analyses are presented as means ± SEMs.

RESULTS

Eleven rats receiving intranigral saline had a mean frequency of 3.7 ± 0.4 VCM/min for the first 30 min postinfusion. There were no significant differences in premeasurement scores between groups. Thirty minutes after infusion, all groups had returned to control levels (data not shown).

Infusions of 8-OH-DPAT produced a dose-dependent depression of VCM frequency with a significant main group effect, $F(4, 29) = 6.1$, $p < 0.01$. Posthoc analysis showed

that all doses of 8-OH-DPAT reduced the VCM frequency in comparison to saline (Table 1) and a linear dose-response relationship was indicated in a regression analysis using AUC 0-20 min as the response variable ($r = -0.65$, $p < 0.0001$, $n = 34$). Coinfusion of UH-301 (40 nmol) with 8-OH-DPAT (1.3 nmol) attenuated the depression of VCM frequency observed after infusion of 1.3 nmol 8-OH-DPAT alone (Table 1). UH-301 by itself did not affect VCM frequency. Infusions of 5-MeO-DMT also lowered VCM frequency with a significant main group effect, $F(2, 23) = 3.7$, $p < 0.05$, but only at the highest concentration (20 nmol). In Fig. 1, AUC 0-20 min for different doses of 8-OH-DPAT and 5-MeO-DMT have been plotted against a baseline of control levels.

In contrast, the nonselective 5-HT agonists TFMPP and mCPP increased VCM frequencies (Table 2) with significant main group effects for VCMs 0-30 min postinfusion, $F(3, 27) = 5.9$, $p < 0.01$ (TFMPP), and $F(3, 25) = 6.1$, $p < 0.01$ (mCPP). Posthoc comparisons showed that the greatest effects were seen after 5 nmol ($p < 0.01$, TFMPP; and $p < 0.05$, mCPP) and 10 nmol ($p < 0.01$, mCPP). Figure 2 illustrates the effect of saline, 8-OH-DPAT (13 nmol), and TFMPP (5 nmol). Low concentrations of the 5-HT_3 agonist 2-Me-5-HT also elevated VCMs, $F(2, 27) = 6.4$, $p < 0.01$. However, another 5-HT_3 agonist (biguanide) was without effect over the range of concentrations used in this experiment. The 5-HT_2/5-HT_{1C} agonist DOB was also without effect on oral behavior.

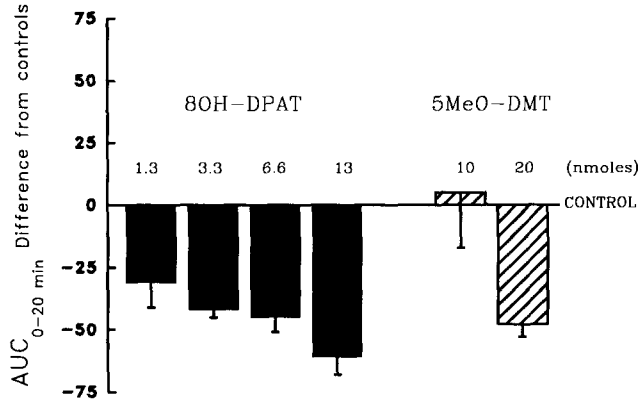

FIG. 1. Difference in the area under the curve (AUC) 0-20 min between saline 0.5 μl (control treatment) and the different doses of 8-hydroxy-2-(di-propylamino)tetralin (8-OH-DPAT) (1.3, 3.3, 6.6, or 13 nmol) or 5-methoxy-*N,N*-dimethyltryptamine hydrogen oxalate (5-MeO-DMT) (10 or 20 nmol) after bilateral intranigral infusion in freely moving rats. The zero line represents control treatment, solid bars 8-OH-DPAT, and hatched bars 5-MeO-DMT.

DISCUSSION

Modern psychiatric treatment of depression, anxiety, and various psychotic states involves an increasing use of compounds that directly affect 5-HT neurotransmission (29). Some of these new drugs have been shown to produce extrapyramidal symptoms in the clinic, notably dystonias and dyskinesias (4,43). The substantia nigra is known to play an important role in the regulation of dyskinesia (13) and also contains

TABLE 1

EFFECTS ON VCM/min (0-30 min) AFTER BILATERAL INTRANIGRAL INFUSION OF THE 5-HT_{1A} AGONISTS 8-OH-DPAT AND 5-MeO-DMT, THE 5-HT_{1A} ANTAGONIST UH-301, AND COMBINATIONS OF 8-OH-DPAT AND UH-301

	Dose	VCMlow	Time Lowest Score (min)	VCMmean
Single drugs				
Saline	–	2.2 ± 0.6	5	3.7 ± 0.4
8-OH-DPAT	1.3	1.0 ± 1.2	1	1.7 ± 0.4 ($p < 0.05$)
8-OH-DPAT	3.3	0.2 ± 0.1	1	1.7 ± 0.4 ($p < 0.05$)
8-OH-DPAT	6.6	0.0 ± 0.0	1,5	1.8 ± 0.4 ($p < 0.05$)
8-OH-DPAT	13	0.0 ± 0.0	1,5,10	1.4 ± 0.6 ($p < 0.05$)
5-MeO-DMT	10	0.5 ± 0.2	5	4.5 ± 0.8
5-MeO-DMT	20	2.1 ± 0.8	5	1.4 ± 0.3 ($p < 0.05$)
UH-301	18	3.8 ± 2.3	5	6.3 ± 1.8
UH-301	40	1.3 ± 0.3	0	3.0 ± 1.3
Drug combinations				
8-OH-DPAT + UH-301	1.3 18	1.9 ± 0.4	30	3.4 ± 0.7
8-OH-DPAT + UH-301	1.3 40	2.6 ± 0.6	5	4.7 ± 0.8*
8-OH-DPAT + UH-301	3.3 18	1.4 ± 0.8	20	2.1 ± 0.5 ($p < 0.05$)
8-OH-DPAT + UH-301	3.3 40	0.4 ± 0.3	0	2.4 ± 0.5

Doses in nmol refer to the amount of drug infused into each SNr. VCMlow is the lowest VCM score (mean ± SEM) observed at any single observation time point (time lowest score) during the 0 to 30-min postinfusion period. VCMmean is calculated on the VCM frequency 0-30 min post infusion. Posthoc Tukey's comparisons to control treatment are shown.

*Differs from 8-OH-DPAT 1.3 nmol, $p < 0.05$.

TABLE 2

EFFECTS ON VCM AFTER BILATERAL INTRANIGRAL INFUSION OF THE 5-HT AGONISTS mCPP, TFMPP, DOB, 2-Me-5HT, AND BIGUANIDE

Drug	Dose	VCMhigh	Time Highest Score (min)	VCMmean
Saline	–	4.6 ± 1.3	20	3.7 ± 0.4
mCPP	5	11.3 ± 2.2	5	6.9 ± 1.0 ($p < 0.05$)
mCPP	10	9.6 ± 2.6	20	7.0 ± 0.6 ($p < 0.01$)
mCPP	20	7.3 ± 1.7	20	5.4 ± 0.9
TFMPP	5	19.3 ± 5.1	15	12.2 ± 2.8 ($p < 0.01$)
TFMPP	10	12.4 ± 5.0	30	8.2 ± 1.8
TFMPP	20	9.7 ± 2.4	10	6.1 ± 1.0
DOB	10	6.6 ± 2.1	30	4.3 ± 0.2
2-Me-5HT	10	7.5 ± 1.2	20	6.7 ± 0.6 ($p < 0.01$)
2-Me-5HT	20	6.0 ± 1.8	15	4.4 ± 0.9
Biguanide	10	9.6 ± 2.9	10	5.7 ± 0.6
Biguanide	20	6.4 ± 2.1	20	4.9 ± 1.4

Doses in nmol refer to the amount of drug infused into each SNr. VCMhigh is the highest VCM score (mean ± SEM) observed at one single observation time point (time highest score) during the 0- to 30-min postinfusion period. VCMmean is calculated on the VCM frequency 0–30 min postinfusion. Posthoc Tukey's comparisons to control treatment are shown.

a dense population of 5-HT receptors (31). In the present study, we showed that infusion of 5-HT agonists into the SNr of rats significantly altered VCM frequency, an easily quantifiable oral behavior with some bearing on drug-induced dyskinesias (15,42). Stimulation of nigral 5-HT receptors with a selective 5-HT_{1A} agonist (8-OH-DPAT) caused a dose-dependent decrease in VCM frequency that could be blocked by the coinfusion of a specific 5-HT_{1A} antagonist (UH-301). Conversely, the nonselective 5-HT agonists TFMPP and mCPP and a 5-HT_3 agonist increased VCM frequency. An agonist acting at 5-HT_{1C} and 5-HT_2 receptors did not alter VCM frequency at the concentrations used in these experiments. Together, these results indicate that activation of 5-HT_{1A} receptors within the substantia nigra reduces VCM frequency whereas stimulation of other subtypes of nigral 5-HT receptors increases VCM frequency.

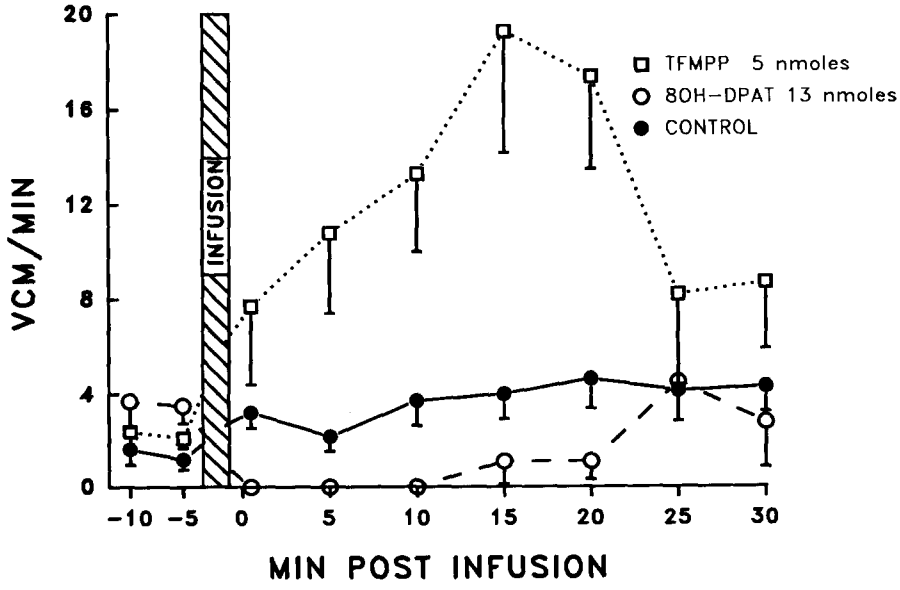

FIG. 2. Mean vacuous chewing movements (VCMs/min ± SEM) observed before and after bilateral intranigral infusion of saline 0.5 ml (control treatment), (*R*)-8-hydroxy-2-(di-propylamino)-tetralin (8-OH-DPAT) 13 nmol or 1-(3-trifluoro-methylphenyl) piperazine (TFMPP) 5 nmol in freely moving rats. Doses refer to the amount of drug infused into each substantia nigra. The hatched area represents the infusion period.

Insights into the possible identity of the receptors responsible for the stimulatory effect of nonspecific 5-HT agonists on VCM frequency come from receptor autoradiographic studies. These studies showed that the overwhelming majority of 5-HT binding sites in the substantia nigra pars reticulata are of the 5-HT_1 subtype [maximal binding density for 5-HT_1 receptors 2,742 fmol/mg protein vs. 29 fmol/mg protein for 5-HT_2 receptors (31)]. Further analysis showed that most (over 70%) of these receptors are of the 5-HT_{1B} subtype with the remainder being 5-HT_{1A} (31). The reduction in VCM frequency following intranigral 5-HT_{1A} agonist infusions observed in the present experiments was most likely due to a direct activation of these 5-HT_{1A} receptors. Further, the failure of ligands with selectivity for 5-HT_{1C} and 5-HT_2 receptors to alter VCM frequency is in good agreement with the known distribution of these receptor subtypes. Because 5-HT_{1B} receptors are located in high concentrations throughout the substantia nigra (31), it is likely that the increase in VCM frequency following infusion of the nonspecific agonists TFMPP and mCPP was due to the activation of 5-HT_{1B} receptors. In fact, both these compounds are thought to interact with some preference for 5-HT_{1B} receptors (22,29). The finding that stimulation of 5-HT_{1B} receptors has effects opposite to that of 5-HT_{1A} activation has parallels in other studies. For instance, mCPP acting as a putative 5-HT_{1B} agonist is known to reduce food intake and elevate body temperature and blood pressure, whereas 5-HT_{1A} agonists increase food intake and produce hypothermia and hypotension (2,23,28,29).

In the present experiment, stimulation of 5-HT_3 receptors gave mixed results. The highly selective 5-HT_3 agonist, biguanide, had no effect on oral behavior while another compound, 2-Me-5-HT, increased VCM frequency. Ligand binding studies focusing on 5-HT_3 receptors showed that this receptor subtype appears to be restricted to limbic structures (24). Because 5-HT_3 receptors have not been detected in the substantia nigra, it is possible that stimulation of oral behavior by 2-Me-5-HT may also be due to activation of 5-HT_{1B} receptors.

In a previous article that examined the role of 5-HT neurotransmission on oral behavior, an increase in chewing after systemic application of certain 5-HT agonists was demonstrated (38). However, unlike the results of the present experiment, a decrease in oral behavior after 5-HT_{1A} agonist administration was not reported. While the precise reason for this discrepancy is unknown, the differences in the results may be related to the method of drug application. In the earlier article (38), it is likely that systemically applied 8-OH-DPAT affected the serotonergic neurons of the dorsal raphé, one region known to contain one of the highest concentrations of 5-HT_{1A} receptors in the brain (31). Electrophysiological studies have shown that activation of 5-HT receptors in this brain area reduces the activity of dorsal raphé 5-HT neurons (1) and reduces 5-HT levels in a number of brain areas (16), including the substantia nigra (10). Consequently, the systemic application of 8-OH-DPAT may have altered nigral 5-HT transmission in two ways: first, through direct interactions with nigral 5-HT_{1A} receptors and second by altering 5-HT release in the substantia nigra, which would affect both 5-HT_{1A} and 5-HT_{1B} receptors. Because these receptors may have opposite effects on oral behavior (results of present experiment), it is possible that the simultaneous stimulation of both receptor subtypes would result in a cancellation of the effect of either receptor subtype. In the present experiment, however, the confounding influence of the nigral afferents originating on dorsal raphé 5-HT neurons was eliminated through the direct infusion of 8-OH-DPAT into the substantia nigra. Using this method, it is possible that a more selective stimulation of 5-HT_{1A} receptors was achieved and a specific role of nigral 5-HT_{1A} receptors was revealed.

Results of previous experiments have also shown that systemic administration of TFMPP and mCPP increased oral behavior with a bell-shaped dose-response curve (38). As oral behavior declined at the higher doses, other behaviors characteristic of 5-HT_{1A} receptor stimulation (17,40) emerged. With regard to oral behavior, similar results were obtained in the present study with an increase in VCM frequency after infusion of lower concentrations of TFMPP and mCPP and no effect after the highest concentrations. However, in contrast to results following systemic administration, the intranigral application of a higher concentration of these compounds did not produce responses characteristic of 5-HT_{1A} receptor stimulation. These results, together with data showing that intranigral infusion of the highly selective 5-HT_{1A} agonist 8-OH-DPAT did not stimulate characteristic 5-HT_{1A} responses like forepaw treading and flat body posture, suggest that these behaviors are not mediated through 5-HT_{1A} receptors located in the substantia nigra. On the other hand, the modulation of oral behavior induced by either systemic or local application of 5-HT agonists appears to be mediated through nigral 5-HT_{1B} receptors. The concentration-dependent decline in VCM frequency observed in the present experiment may be due to the simultaneous activation of both 5-HT_{1A} and 5-HT_{1B} receptors at high drug concentrations.

The data from the present experiment together with accumulating clinical evidence suggests that compounds that interact with 5-HT neurotransmission can affect neural processes that regulate dystonias and dyskinesias. It is also possible that movement disorders associated with other compounds such as neuroleptics whose primary pharmacological action is as DA receptor antagonists (7,35) might involve interactions with nigral 5-HTergic neurotransmission. Exposure to neuroleptics alters both dopaminergic and 5-HT neurotransmission as indicated by changes in DA D_1 and D_2 and 5-HT_1 and 5-HT_2 receptor binding (9,30,44). Neuroleptic-dependent changes in cortical, striatal, and nigral 5-HT_1 receptor binding are accompanied by an increase in motor responsiveness to serotonergic agonists (9). Conversely, 5-HT neurons in the dorsal and median raphé project to the substantia nigra, where they exert an inhibitory influence on dopaminergic neurons (10,11). Changes in 5-HT transmission are also known to influence DA turnover in several brain regions (16), including the substantia nigra (10). Finally, a negative feedback loop between the substantia nigra and the dorsal raphé has been demonstrated by electrophysiological experiments (37). That study showed that electrical stimulation of the substantia nigra inhibits neuronal activity in dorsal raphé presumably through GABAergic afferents. Together, these results suggest that blockade of dopaminergic transmission with classical neuroleptics reduces 5-HT activity by enhancing GABAergic inhibition of 5-HT neurons in the raphé. The result of this inhibition would be an increase in 5-HT receptor number and a subsequent increase in tissue sensitivity in several brain areas, including the substantia nigra. The increase in sensitivity of nigral neurons to 5-HT would result in an exaggerated response to 5-HT release. Therefore, it is possible that dyskinetic symptoms induced by long-term administration of neuroleptics or selective 5-HTergic compounds may be a result of altered 5-HT transmission in the SNr.

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