Direct Injection of 5-HT$_{2A}$ Receptor Agonists into the Medial Prefrontal Cortex Produces a Head-Twitch Response in Rats

DAVID L. WILLINS and HERBERT Y. MELTZER

Department of Psychiatry, Case Western Reserve University, School of Medicine, Cleveland, Ohio

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ABSTRACT

The serotonin (5-HT)$_{2A/C}$ agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-aminoopropane (DOI), the 5-HT$_{2C}$ agonist 6-chloro-2-[1-piperazinyl]-pyrazine and the 5-HT$_{2A}$ partial agonist m-chloro-phenylpiperazine (mCPP) were injected bilaterally into the medial prefrontal cortex of male rats. DOI and mCPP, but not 6-chloro-2-[1-piperazinyl]-pyrazine, elicited a dose-dependent head-twitch response (HTR). DOI-induced HTR had an ED$_{50}$ of 12.8 nmoles/0.5 µl/side and was inhibited by the 5-HT$_{2A}$ antagonists ketanserin and MDL 100,907 but was not blocked by pretreatment with the selective 5-HT$_{2C/2B}$ antagonist SDZ SER 082. The HTR to mCPP demonstrated a bell-shaped dose-response curve with an ED$_{50}$ of 1.5 nmoles/0.5 µl/side and a peak effect after 3 nmoles/side. The response to mCPP was greatly diminished by both ketanserin and MDL 100,907 and was partially reversed by SDZ SER 082. These findings suggest that the HTR produced by the direct injection of serotonergic agonists into the medial prefrontal cortex is, in part, mediated by the activation of 5-HT$_{2A}$ receptors. Pretreatment of rats with the 5-HT$_{1A}$ agonist (±)-8-hydroxy-dipropylaminotetralin hydrobromide inhibited the HTR to DOI. This is consistent with other evidence that suggests a functional antagonism between 5-HT$_{1A}$ and 5-HT$_{2A}$ receptor activation. The HTR to DOI was potentiated by the novel 5-HT$_{1A}$ selective agonist WAY 100,635, which suggests that 5-HT$_{1A}$ receptors tonically regulate this behavioral response to stimulation of cortical 5-HT$_{2A}$ receptors.

The systemic administration of direct as well as indirect 5-HT agonists to rodents has been shown to produce a characteristic HTR (Peroutka et al., 1981; Colpaert and Janssen, 1983; Green et al., 1983; Goodwin and Green, 1985; Darmani et al., 1990a, 1990b, 1992). HTR produced by serotonergic agonists can be blocked by selective 5-HT$_{2}$ receptor antagonists (Lucki et al., 1984; Handley and Singh, 1986). These findings suggest that the HTR is mediated by 5-HT$_{2}$ receptors. Indeed, a strong correlation exists between the potency of serotonin antagonists to inhibit 5-HT$_{2}$ agonist-induced HTR and affinity for the 5-HT$_{2}$ binding site (Peroutka et al., 1981; Ortmann et al., 1982).

The development of highly selective and potent 5-HT$_{2}$ antagonists, along with advanced molecular biological techniques, has led to the classification of serotonin 5-HT$_{2}$ receptors into at least three different subtypes. Current nomenclature defines the 5-HT$_{2A}$ site as that which corresponds to receptors that mediate contractile function in the fundus of the stomach. The 5-HT$_{2C}$ receptors were originally classified as “5-HT$_{1C}$“ receptors. Because of similarities to the 5-HT$_{2}$ receptor family (as determined by molecular biology, pharmacological profiles and links to second messenger systems), these receptors are now classified with the 5-HT$_{2}$ family. 5-HT$_{2A}$ sites are distributed in high density in the cortex as well as in the hypothalamus, caudate putamen and nucleus accumbens (Pazos et al., 1985; Pazos and Palacios, 1985; Hoyer et al., 1992). The corticolimbic distribution of the 5-HT$_{2A}$ receptors has led to the suggestion that these receptors might be critically involved in the neuropathology and treatment of a variety of psychiatric disorders, including anxiety, depression and schizophrenia. Clinical studies have suggested that compounds with antagonist properties at 5-HT$_{2A}$ may possess anxiolytic, antidepressant and antipsychotic properties (Deakin, 1989; Meltzer et al., 1989). The “atypical” antipsychotics, in particular, have a relatively high affinity for 5-HT$_{2A}$ receptors (Meltzer et al., 1989). It is possible, therefore, that the antipsychotic effect of the atypical antipsychotic drugs involves the inhibition of 5-HT$_{2A}$ receptors.

More recently, it was reported that the direct administration of the mixed 5-HT$_{2A/C}$ agonist DOB into the mPFCx in rats produces a dose-dependent increase in the HTR (Gran-
The effect of (±)-DOB was inhibited by pretreatment with ritanserin, a 5-HT₂A₂C antagonist, which suggests that the behavioral response to DOB is mediated by 5-HT₂A or 5-HT₂C receptors. The co-administration of (±)-DOB with the 5-HT₁A agonist 8-OHDPAT was shown to inhibit the HTR, which further suggests that DOB-induced HTR is mediated by 5-HT₂A receptors. Numerous studies have demonstrated a specific, reciprocal regulation of 5-HT₂A receptors by 5-HT₁A receptors (Darmani et al., 1990b; Araneda and Andrade, 1991; Millan et al., 1992; Ashby et al., 1994; Uphouse et al., 1994; Meltzer and Maes, 1995).

In the present study, we evaluated the HTR to a variety of serotonergic agonists administered directly into the mPFCx. One of these, DOI, is structurally similar to the phenylisopropylamine DOB, and two others, mCPP and MK-212, are arylpiperazines. These drugs differ in their selectivity and efficacy at the 5-HT₂A and 5-HT₂C receptors. A pharmacological analysis of the behavioral effects of direct intracortical administration of 5-HT₂ receptor agonists and the selective activation of cortical 5-HT₂A and 5-HT₂C receptors is currently lacking. In addition to characterizing several different 5-HT₂ agonists, we also utilized new, subtype-selective 5-HT₂ receptor antagonists to evaluate the 5-HT₂ receptors in the mPFCx that mediate the HTR produced by the direct administration of 5-HT₂ agonists into this region. Finally, we extended these studies to demonstrate the existence of a regulatory interaction between 5-HT₁A and 5-HT₂A receptors that may serve to modulate behavioral responses to endogenous 5-HT.

Materials and Methods

**Animals and surgery.** Male, Sprague-Dawley rats (150–250 g, Zivic-Miller Labs, Alison Park, PA) were anesthetized with 1 ml/kg (i.p.) of a mixture of ketamine and xylazine in a ratio of 70 to 6. Anesthetized rats were mounted in a stereotaxic frame (Stoelting Inst., Wood Dale, IL), and the skull was exposed. Two 1.0-mm holes were drilled through the bone, bilaterally, above the mPFCx (3.2 mm anterior to bregma and about 0.7 mm lateral to the sagittal suture) (Paxinos and Watson, 1992). Two additional holes were made partially through the bone in the posterior region of the skull, and two small set screws were screwed into the skull. A 21-gauge stainless steel guide cannula was then stereotaxically placed into each hole and lowered to a position exactly 1.0 mm beneath the surface of the skull. The guide cannulas were then anchored to the skull using Krazy Glue Gel and cemented into position with cranioplastic cement (Plastics One, Reannex, Virginia). “Dummy” cannulas, made of stainless steel wire, were inserted into each guide to keep it patent. Each cannula was measured and precut to a length of 10 mm. Following cannula implantation, each rat was individually housed and was allowed 2 to 3 days for recovery from surgery. Throughout the experiments, the animals were housed in a facility with a light cycle of 12 h on, 12 h off, and they had free access to food and water. The ambient temperature in the vivarium was maintained at 23 ± 1°C.

**Drug administration.** Seventy-two hours after surgical implantation of guide cannulas, rats were placed in behavior-monitoring cages (clear polycarbonate, 38 cm × 33 cm × 34 cm) and allowed a minimum of 30 min to habituate. After habituation, the animals were removed from the cages and gently wrapped in a laboratory towel in order to restrain and calm them during drug administration. Animals were positioned in the towel so that the guide cannulas extended through a small hole to allow access to the injection cannula. The dummy cannulas were removed, and an injection cannula was lowered into each guide. Each drug or vehicle was drawn up into a 10-µl Hamilton microsyringe (Hamilton Inst., Reno, NV) that had a 20-cm length of polyethylene tubing (I.D. 0.8 mm) epoxied to the needle barrel. An injection cannula constructed of a 4-cm piece of 21-gauge stainless steel tubing fitted over a 17-mm length of 26-gauge stainless steel tubing was inserted into the other end of the polyethylene tubing. The injection cannula was cut so that 14 mm of the 26-gauge stainless steel tubing was exposed beyond the end of the 21-gauge tubing. This would allow 4 mm of the injection cannula to protrude from the end of the 10-mm guide cannula that had been surgically implanted 1 mm below the surface of the skull. In this way, drugs could be administered directly into the mPFCx, at a depth of 5 mm beneath the surface of the skull. Drug was administered at a rate of 0.5 µl/min in a total volume of 0.5 µl-side. The injection cannula was then removed, and a dummy cannula was reinserted into each guide. Each animal was then returned to the observation cage, and behavior was monitored for the following 30 min.

For experiments that included a second drug treatment, the drugs were administered either i.p. or s.c. 10 min into the habituation period (20 minutes prior to intracerebral injection). After each experiment, the rats were deeply anesthetized with chloral hydrate and sacrificed by decapitation. Brains were immediately removed and placed in a solution of 4% formaldehyde in water. Then, 24 to 48 h later, fixed brains were cut on a refrigerated microtome, and injection sites were verified histologically from 40-µm coronal sections. In all experiments, each subject was used only once per experiment before dissection. Data from animals in which the needle tracks were found to terminate outside of the mPFCx were discarded (fig. 1). All animal use procedures were in strict accordance with the PHS Guide for Care and Use of Laboratory Animals and were approved by the Case Western Reserve University Institutional Animal Care and Use Committee.

**Behavioral observation.** After drug administration (see above), the number of head twitches observed in each 5-min period was recorded for a total of 30 min. In addition, other stereotyped behaviors (including locomotor activity, sniffing, grooming and rearing) were observed and noted.

**Drugs.** The following drugs and chemicals were used in this study: DOI and 8-OHDPAT (Research Biochemicals Inc., Natick, MA), MK-212 (Merck, Sharpe and Dome, Wilmington, DE), mCPP (Aldrich Chemical Co., Milwaukee, WI), MDL 100,907 (Merrell-Dow Pharmaceuticals, Cincinnati, Ohio), SDZ SER 082 (Sandoz, Basel, Switzerland) and WAY 100,635 (Wyeth-Ayerst, Princeton, NJ). All drugs were dissolved in double-distilled demineralized water.

**Data analysis.** Unless otherwise noted, all data are expressed as the mean ± S.E.M. of the absolute number of head twitches observed in the 30-min observation period immediately after the intracranial administration of drugs or vehicle. The ED₅₀ for DOI and the half-maximal response to mCPP were calculated using the following equation:

\[
E = \frac{(E_{\text{max}} \times \text{Dose})}{(\text{ED}_{\text{50}} + \text{Dose})} 
\]

Data were analyzed using Student’s t test or a Mann-Whitney Rank Sum test for significance with a minimal level of P < .05 accepted as significant.

**Results**

The effect of direct, bilateral administration of 5-HT₄ agonists into the mPFCx on the production of HTR. DOI and mCPP, administered directly into the mPFCx, elicited a maximal HTR within the first 5-min observation period (fig. 2). The response had a duration of approximately 30 min, after which time the response was not
significantly greater than that seen in control animals (fig. 2).

Bilateral administration of DOI into the mPFCx produced a dose-dependent activation of the HTR. At doses of 2.8, 8.4 and 28 nmoles/0.5 μl/side, rats demonstrated an average of 9.6, 32.6, and 42.6 head twitches, respectively (fig. 3). The responses to both the 8.4- and the 28-nmole doses of DOI were significantly greater than the response to saline alone (P < .01, fig. 3). The ED₅₀ for the HTR to DOI was calculated to be 12.8 nmoles/side by nonlinear regression analysis.

The bilateral administration of mCPP into the mPFCx at doses of 1, 3, and 8 nmoles/side produced an average of 18.6, 46.8, and 26.3 head twitches, respectively. Each of these responses was significantly greater than that of vehicle-injected control animals (fig. 3). A dose of 30 nmoles of mCPP, administered bilaterally into the mPFCx, significantly enhanced the HTR in the first 5-min observation period, but by 10 min this response was no greater than that observed in control animals (fig. 2). The total number of head twitches produced by 30 nmoles of mCPP was not greater than that observed in vehicle-treated animals. The half-maximal response to mCPP for the initial phase of mCPP-induced HTR was estimated to be 1.52 nmoles using nonlinear, least-squares regression analysis with the maximal response equal to that produced by a 3-nmole dose of mCPP. Thus mCPP was approximately 8.5 times more potent than DOI in producing the HTR. Rats injected with MK-212 bilaterally into the mPFCx at doses of 3, 8.4, 17 or 30 nmoles/0.5 μl/side demonstrated a nonsignificant increase in the HTR (fig. 3).

Fig. 1. Representative injection sites for the intracranial administration of drugs. ○, sites of drug injection (as determined from needle tracks) that were within the mPFCx. ◊, sites of drug injection in which the injection cannula terminated outside of the mPFCx. HTR data from animals in which either the right or the left injection cannula was determined to have terminated outside of the mPFCx were excluded from the study. The sites shown are derived from animals used in generating the 5-HT agonist dose-response data (figs. 2 and 3). Illustrations are adapted from the atlas of Paxinos and Watson (1992). Measurements in millimeters refer to distance from bregma. aca, anterior commissure, anterior; Acb, accumbens nu; aci, anterior commissure, intrabulbar; Cg1, cingulate cortex, area 1; Cg3, cingulate cortex, area 3; Cl, claustrum; DP, dorsal peduncular cortex; fmi, forceps minor corpus callosum; Fr2, frontal cortex, area 2; IL, infralimbic cortex; Io, lateral olfactory tracts; MO/VO, medial orbital and ventral orbital cortex; RF, rhinal fissure.

Fig. 2. Time course for the production of the HTR by 5-HT₂A agonists administered bilaterally into the mPFCx. Each data point represents the mean ± S.E.M. of at least six determinations. A) The time course of DOI-induced HTR. DOI 8.4 nmoles [P < .05 at all time-points except 15 min (not significant)]; DOI 28 nmoles [P < .05 at all time-points except 15 min (not significant)]. B) The time course of mCPP-induced HTR. mCPP 1 nmole [P < .05 for all time-points except 15, 25 and 30 min (not significant)]; mCPP 3 nmoles [P < .05 for all time-points except 25 and 30 min (not significant)]; mCPP 8 nmoles (P < .05 for all time-points except 15 and 30 min (not significant)]; mCPP 30 nmoles (P < .01 for 5 min time-point).
Effect of subtype-selective 5-HT₂ antagonists on HTR. Ketanserin pretreatment (2.5 mg/kg s.c.) completely inhibited the HTR produced by DOI (6 ± 2, n = 6, fig. 4). Ketanserin alone had no effect on the HTR in vehicle-injected controls. In addition, other behaviors, such as locomotor activity and stereotypy, did not appear to be affected by the presence of ketanserin. Pretreatment with the selective 5-HT₂ₐ antagonist MDL 100,907 (0.1 mg/kg s.c.) also inhibited the HTR to DOI (fig. 4), with no discernible effect on basal locomotor or stereotypical behavior. Pretreatment with 0.3 mg/kg (s.c.) of the selective 5-HT₂ₐ antagonist SDZ SER 082 did not alter the DOI-induced HTR (fig. 4). This dose of SDZ SER 082 did not affect behavior in rats given this drug alone (data not shown).

The HTR elicited by 3 nmoles/0.5 μl/side of mCPP, a dose that produced a maximal HTR (fig. 3), was significantly reduced by ketanserin (2.5 mg/kg s.c.), by MDL 100,907 (0.1 mg/kg s.c.) and by SDZ SER 082 (0.3 mg/kg s.c.) (fig. 5).

5-HT₁A receptors modulate DOI-induced HTR. Pretreatment with the 5-HT₁A selective agonist 8-OHDPAT (100 μg/kg s.c.) completely inhibited the HTR produced by DOI (fig. 6). The inhibitory effect of 8-OHDPAT on DOI-induced HTR was reversed by the selective 5-HT₁A antagonist WAY 100,635 (100 μg/kg s.c.). WAY 100,635 also potentiated the

Fig. 3. Dose-response curve for the production of a HTR by 5-HT agonists. The ED$_{50}$ for DOI was estimated to be 12.8 nmoles, calculated as an internal ED$_{50}$ (base line to maximal response). The dose of mCPP producing a half-maximal response, in the primary (upward) phase of the dose-response curve, was estimated to be 1.3 nmoles. Vehicle injections elicited an average of 5.7 ± 2.0 twitches in 30 min. Each value represents the mean ± S.E.M. of the total HTR from 6 to 8 animals. * P < .01 with respect to vehicle-injected controls.

Fig. 4. The effect of pretreatment of animals with 5-HT₂ antagonists on HTR produced by bilateral, intra-mPFCx injection of DOI (8.4 nmoles/0.5 μl/side). Each antagonist or saline was administered 20 min before intracortical injection of DOI at the following doses: saline, 0.9%, 1 ml/kg (i.p., n = 6); ketanserin, 2.5 mg/kg (i.p., n = 6); MDL 100,907, 0.1 mg/kg (s.c., n = 4); SDZ SER 082, 0.3 mg/kg (s.c., n = 6). * P < .001 with respect to DOI group; ** P = .005 with respect to DOI group; † P = .016 with respect to vehicle.

Fig. 5. The effect of pretreatment of animals with 5-HT₂ antagonists on HTR produced by bilateral, intra-mPFCx injection of mCPP (3.0 nmoles/0.5 μl/side). Each antagonist or saline was administered 20 min before intracortical injection of DOI at the following doses: saline, 0.9%, 1 ml/kg (i.p., n = 5); ketanserin, 2.5 mg/kg (i.p., n = 5); MDL 100,907, 0.1 mg/kg (s.c., n = 5); SDZ SER 082, 0.3 mg/kg (s.c., n = 5). * P < .001 with respect to mCPP; ** P = .006 with respect to mCPP group; † P < .001 with respect to vehicle; †† P = .003 with respect to vehicle.
5-HT2A rather than 5-HT2C receptors.

5-HT2A receptors. This finding suggests that head-twitch of MK-212 ranging from 3 to 30 nmoles/side did not produce a HTR. Direct, bilateral, intracortical administration of doses produced by DOI could be mediated at the 5-HT2A or the 5-HT2C subtypes of 5-HT receptors, although the DOI-induced HTR was reversed by the 5-HT2A receptor antagonist ketanserin and MDL 100,907 suggests that the response is preferentially mediated by the activation of 5-HT2A receptors in the cerebral cortex (Conn et al., 1995). The dose of SDZ SER 082 used in the present study (0.3 mg/kg s.c.) is equivalent to the ID50 of the compound for inhibition of the hypophagic effect produced by MK-212 in rats and is triple the dose that was demonstrated to reduce significantly MK-212-mediated increases in serum ACTH (Nolzul et al., 1995). Finally, a recent study has demonstrated that a variety of selective 5-HT2A antagonists blocked the HTR to systemically administered DOI and that the relative potency of these antagonists was highly correlated with their affinity at 5-HT2A receptors, but not with their affinity for 5-HT2C sites (Schreiber et al., 1995). Taken together, these findings strongly support the conclusion that the DOI-induced HTR is mediated by a selective activation of 5-HT2A receptors.

Interestingly, the direct, bilateral administration of the phenylpiperazine derivative mCPP into the rat mPFCx also demonstrated to reverse d-amphetamine-induced slow- ing of the firing of A9 and A10 DA neurons (Sorensen et al., 1993). Additionally, this dose of MDL 100,907 is 3-fold lower than the ED50 value for inhibition of d-amphetamine-stimu- lated locomotor activity (Sorensen et al., 1993). The inhibition of DOI-induced head twitch by a low dose of MDL 100,907 suggests that the response is preferentially mediated by the activation of 5-HT2A rather than 5-HT2C receptors. This finding, together with the observation that MK-212 did not produce a HTR, strengthens the conclusion that the DOI-induced HTR is not mediated by 5-HT2C receptors in the mPFCx.

Further evidence that the HTR produced by DOI is not mediated by the activation of 5-HT2C receptors is provided by the finding that the selective 5-HT2C receptor antagonist SDZ SER 082 did not inhibit the response to DOI. SDZ SER 082 has been shown, in autoradiographic studies, to displace 5-HT2C binding from human choroid plexus at a 100-fold lower concentra- tion than from 5-HT2A sites in human claustrum (Waebel and Palacios, 1994). In binding studies, SDZ SER 082 had a 40-fold greater affinity for human recombinant 5-HT2C receptors (pKd = 7.8) than for 5-HT2A receptors (pKd = 6.2) (Nolzul et al., 1995). The dose of SDZ SER 082 used in the present study (0.3 mg/kg s.c.) is equivalent to the ID50 of the compound for inhibition of the hypophagic effect produced by MK-212 in rats and is triple the dose that was demonstrated to reduce significantly MK-212-mediated increases in serum ACTH (Nolzul et al., 1995). Finally, a recent study has demonstrated that a variety of selective 5-HT2A antagonists blocked the HTR to systemically administered DOI and that the relative potency of these antagonists was highly corre- lated with their affinity at 5-HT2A receptors, but not with their affinity for 5-HT2C sites (Schreiber et al., 1995). Taken together, these findings strongly support the conclusion that the DOI-induced HTR is mediated by a selective activation of 5-HT2A receptors.

Interestingly, the direct, bilateral administration of the phenylpiperazine derivative mCPP into the rat mPFCx also elicited a HTR (figs. 2 and 3). mCPP has been shown to be an antagonist at 5-HT2A receptors in the cerebral cortex (Connn and Sanders-Bush, 1987) and to block the HTR produced by quipazine (Simansky and Schechter, 1988). Recently, however, mCPP has been shown to behave as a partial agonist at cloned 5-HT2A receptors (Grotewiel et al., 1994). It is therefore possible that the HTR to mCPP is a result of the activa- tion of 5-HT2A receptors. The dose-response curve for the mCPP-induced HTR was a “bell-shaped” dose-response

**Discussion**

The major finding of the present study was that the direct, bilateral administration of the 5-HT agonists DOI and mCPP into the mPFCx of rats produces HTR. This response was dose-dependent and appears to be mediated by the activation of 5-HT2A receptors. DOI has similar affinity and efficacy at both the 5-HT2A and the 5-HT2C subtypes of 5-HT receptors, whereas the HTR produced by DOI could be mediated at the 5-HT2A or the 5-HT2C receptor. In order to determine the relative roles of 5-HT2A and 5-HT2C receptors in the production of the HTR to DOI, we tested the ability of MK-212, a 5-HT2A antagonist at 5-HT2A receptors, to reduce significantly MK-212-mediated increases in serum

![Graph](image-url)
curve. It may be that at different doses, mCPP, which has been demonstrated to have significant affinity for a variety of receptors in addition to 5-HT2A sites, including 5-HT2C (Curzon and Kennett, 1990; Choudhary et al., 1992), 5-HT1B and 5-HT1A receptors (Sills et al., 1984; Asarch et al., 1985; Hamon et al., 1986), may actually be activating receptors that are functionally antagonistic to the response to 5-HT2A receptor activation (e.g., 5-HT1A sites).

In much the same manner as previously demonstrated for DOI, pretreatment of animals with either ketanserin or MDL 100,907 was shown to decrease the HTR produced by mCPP (fig. 5). This suggests that the activation of 5-HT2A receptors is required for the production of a HTR by mCPP. Although the HTR to DOI was unaffected by pretreatment with the selective 5-HT2C receptor agonist SDZ SER 082, the HTR to mCPP was significantly reduced by this agent. Because the dose-response curve to mCPP is an inverted-U function, and because the dose of mCPP used in the evaluation of antagonist effects was a dose that produced a maximal HTR, the direction of the curve shift produced by SDZ SER 082 cannot be determined. Further study would be required to determine whether this effect reflects an inhibition of the mCPP response or, alternatively, a potentiation of the response, perhaps through some functional interaction between 5-HT2A and 5-HT2C receptors. The fact that SDZ SER 082 had any effect at all on the mCPP response without altering behavior on its own further supports the conclusion that mCPP-induced HTR is not solely mediated by the activation of 5-HT2A sites in the mPFCx.

Several studies have suggested that the frontal cortex may not be involved in the HTR produced by systemically administered 5-HT agonists. Lucki and Minugh-Purvis (1987) reported that ablation of the frontal cortex did not inhibit the HTR to either the 5-HT precursor 5-HTP or the direct-acting 5-HT agonist quipazine. Bedard and Pycock (1977) reported that knife cuts at the level of the caudal diencephalon decreased the HTR and that cuts at the level of the posterior commissures eliminated the HTR entirely. Transection at the level of the anterior commissures, however, had no effect on the HTR to 5-HTP. These authors concluded that the ability of 5-HT agonists to elicit a “wet-dog” shake did not depend on the frontal regions of the cortex. Despite these findings, which suggest that the HTR to systemically administered 5-HT agonists is not critically dependent on processes in the frontal cortex, the present study demonstrates that the direct activation of 5-HT2A receptors in the mPFCx can produce a HTR. Although it is possible that after injection directly into the mPFCx, the drugs studied here could have entered the cerebrospinal circulation and thus come into contact with receptors in the spinal cord, the fact that no HTR was observed in animals in which DOI was injected outside of the mPFCx suggests that this is unlikely. In addition, the rapid onset of the drug-induced HTR suggests that the locus of the response to intracortical drug administration is within the mPFCx. Finally, the production of a HTR through the activation of central 5-HT sites is consistent with the report that i.c.v. administration of the 5-HT neurotoxin 5,7-dihydroxytryptamine increased the HTR produced by the 5-HT2A agonist 5-methoxy-N,N-dimethyltryptamine as well as the Bmax for [3H]ketanserin binding in the cortex of adult male mice (Heal et al., 1985). Although this does not preclude a spinal locus for the HTR to systemically admin-
receptors. These findings support a role for 5-HT₂A receptors in the mPFCx in 5-HT-mediated behavior and suggest that a critical analysis of 5-HT₂A receptor function in this region may yield pertinent information about the role of this region in the mechanism of action of new, atypical anxiolytic, antidepressant, and antipsychotic drugs.

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References


Send reprint requests to: David L. Willins, Ph.D., University Hospitals, Cleveland, Hanna Pavilion, Rm. B58, 11100 Euclid Ave., Cleveland, Ohio 44106.