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Discriminative Stimulus Effects of 1-(2,5-Dimethoxy-4-Methylphenyl)-2-Aminopropane in Rhesus Monkeys: Antagonism and Apparent pA_2 Analyses

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ABSTRACT

Discriminative stimulus effects of the serotonin (5-HT) receptor agonist 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) have been studied in rats and, more recently, in rhesus monkeys. This study examined DOM, 2,5-dimethoxy-4-(*n*)-propylthiophenethylamine (2C-T-7), and dipropyltryptamine hydrochloride (DPT) alone and in combination with three antagonists, MDL100907 [(±)2,3-dimethoxyphenyl-1-[2-(4-piperidine)-methanol]], ketanserin [3-[2-[4-(4-fluorobenzoyl)piperidin-1-yl]ethyl]-1*H*-quinazoline-2,4-dione], and ritanserin [6-[2-[4-[bis(4-fluorophenyl)methylidene]piperidin-1-yl]ethyl]-7-methyl-[1,3]thiazolo[2,3-*b*]pyrimidin-5-one], to identify the 5-HT receptor subtype(s) that mediates the discriminative stimulus effects of these 5-HT receptor agonists. Four adult rhesus monkeys discriminated between 0.32 mg/kg s.c. DOM and vehicle while responding under a fixed ratio 5 schedule of stimulus shock termination. DOM, 2C-T-7, and DPT dose-dependently increased responding on the DOM-associated lever. MDL100907 (0.001–0.01 mg/kg), ketanserin (0.01–0.1 mg/kg), and ritanserin (0.01–0.1 mg/kg) each shifted the dose-response curves of DOM, 2C-T-7, and DPT rightward in a parallel manner. Schild analysis of each drug combination was consistent with a simple, competitive, and reversible interaction. Similar apparent affinity (pA_2) values were obtained for MDL100907 in combination with DOM (8.61), 2C-T-7 (8.58), or DPT (8.50), for ketanserin with DOM (7.67), 2C-T-7 (7.75), or DPT (7.71), and for ritanserin with DOM (7.65), 2C-T-7 (7.75), or DPT (7.65). Potency of antagonists in this study was correlated with binding affinity at 5-HT_{2A} receptors and not at 5-HT_{2C} or α_1 adrenergic receptors. This study used Schild analysis to examine receptor mechanisms mediating the discriminative stimulus effects of hallucinogenic drugs acting at 5-HT receptors; results provide quantitative evidence for the predominant, if not exclusive, role of 5-HT_{2A} receptors in the discriminative stimulus effects of DOM, 2C-T-7, and DPT in rhesus monkeys.

Phenethylamines and tryptamines are two classes of drugs that act at serotonin (5-HT) receptors and can produce hallucinations; in general, agonists from these two classes have similar but not identical behavioral and neurochemical effects. For example, many phenethylamines bind relatively nonselectively to 5-HT_{2A} and 5-HT_{2C} receptors and have comparatively lower (e.g., 1000-fold) affinity for other (e.g., 5-HT_{1A}) 5-HT receptors. Tryptamines, on the other hand, often display higher affinity than phenethylamines for 5-HT_{1A} receptors (for review, see Nichols, 2004; Fantegrossi et al., 2008a) and comparatively lower affinity for 5-HT_{2A} and 5-HT_{2C} receptors. Despite differences between phenethylamines and tryptamines in their binding selectivity for different 5-HT receptors, with few exceptions (e.g., Winter et al., 2000), agonists from these chemical classes have similar effects that seem to be mediated predominantly by 5-HT_{2A} receptors (e.g., Vollenweider et al., 1998).

Drug discrimination is used to study receptor mechanisms that mediate the effects of drugs from a variety of pharmacologic classes. Many drugs with hallucinogenic effects in humans have agonist actions at 5-HT receptors, and among

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ABBREVIATIONS: 5-HT, serotonin; DOM, 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane; MDL100907, (±)2,3-dimethoxyphenyl-1-[2-(4-piperidine)-methanol]; ketanserin, 3-[2-[4-(4-fluorobenzoyl)piperidin-1-yl]ethyl]-1*H*-quinazoline-2,4-dione; ritanserin, 6-[2-[4-[bis(4-fluorophenyl)-methylidene]piperidin-1-yl]ethyl]-7-methyl-[1,3]thiazolo[2,3-*b*]pyrimidin-5-one; 2C-T-7, 2,5-dimethoxy-4-(*n*)-propylthiophenethylamine; DPT, dipropyltryptamine hydrochloride; FR, fixed ratio; CL, confidence limit; MK-212, 6-chloro-2(1-piperazinyl) pyrazine hydrochloride.

those drugs, the discriminative stimulus effects of the phenethylamine 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) have been studied extensively in rodents (Glennon et al., 1982; Fiorella et al., 1995a) and, more recently, in nonhuman primates (Li et al., 2008). Converging lines of evidence indicate that despite the nonselective binding of DOM to 5-HT_{2A} and 5-HT_{2C} receptors, the discriminative stimulus effects of DOM seem to be mediated predominantly by 5-HT_{2A} receptors inasmuch as drugs that are antagonists at 5-HT_{2A} receptors often block the discriminative stimulus effects of DOM (e.g., Glennon et al., 1983). Moreover, the ability of drugs to antagonize the discriminative stimulus of DOM is positively correlated with binding affinity at 5-HT_{2A} receptors (Fiorella et al., 1995b). However, there are conditions under which other receptors seem to play a role in the discriminative stimulus effects of DOM. For example, the nonselective 5-$HT_{2A/2C}$ receptor agonist MK-212 substitutes for the discriminative stimulus effects of DOM in rats, and this effect of MK-212 is not fully antagonized by the 5-HT_{2A} receptor antagonist pirenperone (Fiorella et al., 1995c). Collectively, these data suggest that other (e.g., 5-HT_{2C}) receptors might play a role, directly or by modulation, in the discriminative stimulus effects of DOM and related 5-HT receptor agonists.

This study investigated the receptor mechanisms that mediate the discriminative stimulus effects of DOM and related drugs in rhesus monkeys. Each of three 5-HT receptor agonists was studied alone and in combination with each of three other drugs that are known to have antagonist actions at 5-HT_{2A} receptors: MDL100907, ketanserin, and ritanserin. Schild analysis has been used to examine receptor mechanisms for drugs acting at other receptors (Dykstra et al., 1988; Dykstra, 1990; France et al., 1990; Gerak and France, 2007) and, in the current study, was used to quantitatively compare dose-response curves from combinations of 5-HT receptor agonists and antagonists. MDL100907 and ketanserin have higher affinity at 5-HT_{2A} compared with 5-HT_{2C} receptors, whereas ritanserin has similar affinity at 5-HT_{2A} and 5-HT_{2C} receptors (NIMH Psychoactive Drug Screening Program, http://pdsp.med.unc.edu). If 5-HT_{2C} receptors are involved in the discriminative stimulus effects of DOM, then antagonists acting at 5-HT_{2A} and 5-HT_{2C} receptors (e.g., ritanserin) should more effectively block the effects of DOM compared with antagonists acting selectively at 5-HT_{2A} receptors (e.g., MDL100907). The 5-HT_{2A} receptor agonists studied included DOM, 2,5-dimethoxy-4-(*n*)-propylthiophenethylamine (2C-T-7), and dipropyltryptamine hydrochloride (DPT). 2C-T-7 is a "designer" phenethylamine with hallucinogenic activity and high affinity at 5-HT_{2A} and 5-HT_{2C} receptors; however, the behavioral effects of 2C-T-7, including discriminative stimulus effects in nonhuman primates (Li et al., 2008), seem to be mediated by 5-HT_{2A} receptors (Fantegrossi et al., 2005). DPT, a tryptamine with hallucinogenic activity, recently was shown to have agonist activity at 5-HT_{2A} and 5-HT_{1A} receptors (Li et al., 2007; Fantegrossi et al., 2008b).

Materials and Methods

Subjects. Four adult rhesus monkeys weighing between 4 and 8 kg and previously trained to discriminate between saline and 0.32 mg/kg DOM (Li et al., 2008) were housed individually with unlimited access to water. Primate chow (Harlan Teklad High Protein Monkey Diet; Harlan Teklad, Madison, WI), fresh fruit, and peanuts were provided after daily sessions in amounts sufficient to maintain normal, age- and gender-appropriate weights. Monkeys were maintained on a 14-/10-h light/dark cycle. The animals used in these studies were maintained in accordance with the Institutional Animal Care and Use Committee, The University of Texas Health Science Center at San Antonio, and with the *Guide for Care and Use of Laboratory Animals* (Institute of Laboratory Animal Resources, National Research Council, 1996).

Apparatus. During experimental sessions, subjects were seated in chairs (model R001; Primate Products, Inc., Woodside, CA) that provided restraint at the neck and arms and were placed within ventilated, sound-attenuating chambers. Chambers were equipped with response panels, each containing two stimulus lights and two response levers. The feet of monkeys were placed in shoes that were mounted to the front of chairs and equipped with brass electrodes to which a brief (250 ms, 3 mA) electric shock could be delivered from AC generators. Experiments were controlled and data recorded with a microprocessor and commercially available interface (MED Associates, St. Albans, VT).

Procedure. Daily training sessions comprised two to six 15-min cycles, with each cycle starting with a 10-min timeout period, during which stimulus lights were not illuminated and responding had no programmed consequence. This timeout period was followed by a 5-min response period during which stimulus lights were illuminated above the levers and a schedule of stimulus shock termination was active. Monkeys could extinguish stimulus lights and postpone scheduled shock for 30 s by responding five times [fixed ratio (FR) 5] consecutively on the lever designated correct by an injection administered during the 1st min of the cycle (e.g., right lever, saline; left lever, DOM). Incorrect responses reset the FR requirement on the correct lever. Failure to satisfy the FR requirement within 30 s resulted in the delivery of a brief (250 ms, 3 mA) stimulus. Thereafter, shock was delivered every 30 s until the response requirement was satisfied, the cycle ended, or a total of four shocks were delivered, whichever occurred first.

For drug training sessions, monkeys received an injection of 0.32 mg/kg s.c. DOM before one cycle followed by one sham (no injection) cycle. For vehicle training sessions, monkeys received an injection of saline (subcutaneously) before one cycle followed by between one and five sham (no injection) cycles. Monkeys had previously satisfied the following criteria for five consecutive or six of seven sessions (Li et al., 2008): at least 80% of the total responses on the correct lever and fewer than five responses (one FR requirement) on the incorrect lever before completion of the FR on the correct lever. Thereafter, monkeys were tested every 3rd day provided that the testing criteria were satisfied during intervening training sessions. If monkeys failed to satisfy these criteria, testing was postponed until the criteria were satisfied for two consecutive training sessions.

Test sessions were similar to training sessions, except that five consecutive responses on either lever postponed shock and increasing doses of drug were administered across cycles. For substitution studies, saline was administered in the first cycle, followed by increasing doses of drug in subsequent cycles, with the cumulative dose increasing by 0.25 or 0.5 log units per cycle. Drugs were studied up to doses that occasioned greater than 80% responding on the DOM lever. For antagonism studies, a single dose of antagonist was administered 5 min before the start of the first cycle.

Data Analyses. Drug discrimination data are expressed as a percentage of the total responses made on the DOM-paired lever averaged among four monkeys (±1 S.E.M.) and plotted as a function of dose. Rate of lever pressing is plotted as the average (±1 S.E.M.) number of responses per second on both levers. The control response rate is the average of the five vehicle training sessions before the test.

Doses of test drugs to occasion 50% drug lever responding (ED_{50}) and 95% confidence limits (CLs) were estimated using interpolation

or linear regression using the portion of the dose-effect curve spanning 50% drug-lever responding. Dose ratios were determined for each monkey by dividing the ED_{50} values for each agonist (DOM, 2C-T-7, and DPT) studied in combination with an antagonist (MDL100907, ketanserin, and ritanserin) by the ED_{50} values for each agonist studied alone. Schild analyses were conducted as described previously (e.g., Li et al., 2008) using the method of Arunlakshana and Schild (1959). Schild plots were constructed by plotting the log of the dose ratio (agonist with antagonist divided by agonist alone) − 1 as a function of the negative log dose of antagonist (moles per kilogram). Straight lines were simultaneously fitted to the individual Schild plots using GraphPad Prism version 5.00 for Windows (GraphPad Software Inc., San Diego, CA) and the following equation: log (dose ratio − 1) = −log (molar dose of antagonist) × slope + intercept. Apparent affinity (pA_2) values and 95% CLs with unconstrained slopes and, when appropriate, with slopes constrained to −1 (unity) were determined for each agonist and antagonist combination. Slopes of Schild plots were considered to conform to unity when the 95% CL included −1 and did not include 0 (e.g., Paronis and Bergman, 1999).

Drugs. The compounds used in this study were as follows. DOM and 2C-T-7 were obtained from the National Institute on Drug Abuse (Research Technology Branch, Rockville, MD); DPT and MDL100907 were synthesized as described previously (Ullrich and Rice, 2000); and ketanserin tartrate and ritanserin were purchased from Sigma-Aldrich (St. Louis, MO). MDL100907 was dissolved in 20% dimethyl sulfoxide (v/v) and saline; other drugs were dissolved in sterile 0.9% saline. Doses are expressed as the form of the drug listed above in milligrams per kilogram of body weight or in Schild plots as moles per kilogram. Injection volumes were 0.1 to 1.0 ml.

Results

DOM, 2C-T-7, and DPT increased responding on the DOM associated lever in a dose-related manner (Fig. 1, top), with the largest dose of each occasioning more than 90% DOM-lever responding [DOM, ED_{50} (95% CL) = 0.158 (0.117, 0.194) mg/kg; 2C-T-7, 0.156 (0.145, 0.167) mg/kg; and DPT, 0.639 (0.436, 0.817) mg/kg]. DOM and 2C-T-7 were similar in potency, and both were 4-fold more potent than DPT. None of the compounds markedly altered rate of lever pressing at the doses studied (Fig. 1, bottom).

MDL100907 (Fig. 2, left), ketanserin (Fig. 2, middle), and ritanserin (Fig. 2, right) antagonized the discriminative stimulus effect of all three agonists, in each case shifting the dose-response curves to the right in a dose-related manner. For example, under-control condition doses of 0.32 to 1.0 mg/kg DOM, 0.32 mg/kg 2C-T-7, and 1.0–3.2 mg/kg DPT occasioned greater than 90% drug lever responding (filled symbols, top, middle, and bottom, respectively, Fig. 2); in monkeys that received 0.01 mg/kg MDL100907, doses of 3.2 mg/kg DOM, 3.2 mg/kg 2C-T-7, and 10 mg/kg DPT were required to produce at least 90% responding on the DOM lever (triangles, left, Fig. 2). In the presence of larger doses of antagonists, larger doses of agonists were required to obtain responding on the drug lever. For example, after administration of 0.1 mg/kg ritanserin, doses of 5.6 mg/kg DOM, 3.2 2C-T-7, and 10.0 mg/kg DPT were required to obtain greater than 90% drug lever responding (open circles, right, Fig. 2). For all drug combinations, the antagonism was surmountable, with larger doses of agonists occasioning responding on the DOM-associated lever. When administered alone, none of the antagonists occasioned responding on the DOM associated lever (points above "V"; Fig. 2, all panels).

The same data shown in Fig. 2 as dose-response curves are

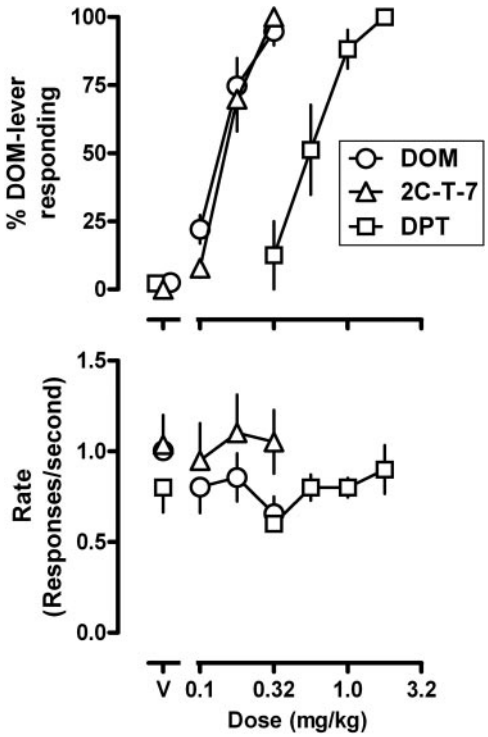

Fig. 1. Discriminative stimulus and rate effects of DOM, 2C-T-7, and DPT in four rhesus monkeys discriminating between vehicle and 0.32 mg/kg DOM. Abscissae, dose in milligrams per kilogram of body weight; V, vehicle. Ordinates, mean (±S.E.M.) percentage of responses on the DOM lever (top) and mean (±S.E.M.) rate of responding in responses per second (bottom).

presented in Fig. 3 as Schild plots, expressing the magnitude of antagonism (ordinate; log [dose ratio − 1]) as a function of the −log of antagonist dose (abscissa). The similarity among the three regression lines in each panel (i.e., for each antagonist combined with each of three different agonists) reflects the similar potency for each antagonist in attenuating the discriminative stimulus effects of DOM, 2C-T-7, and DPT. The intercept of each regression line with the horizontal dashed line (0 on the ordinate) indicates the apparent pA_2 or estimated dose of antagonist to shift the agonist dose-response curve 2-fold to the right. The apparent pA_2 values were similar for each antagonist studied in combination with each of the three agonists (Table 1). For example, the pA_2 values (unconstrained slopes) for MDL100907 were as follows: 8.77 with DOM, 8.59 with 2C-T-7, and 8.62 with DPT. None of the slopes of the Schild regression lines was significantly different from −1 (unity); thus, Table 1 also shows apparent pA_2 values determined with slopes constrained to −1. With the constrained slope, the pA_2 values for MDL100907 were as follows: 8.61 with DOM, 8.50 with 2C-T-7, and 8.58 with DPT. Overall, MDL 100907 was 7.1- and 7.6-fold more potent than ketanserin and ritanserin, respectively, in antagonizing the discriminative stimulus effects of DOM, 2C-T-7, and DPT.

Discussion

Reliable stimulus control between DOM and saline was maintained in rhesus monkeys responding under a two-choice, multiple-cycle, cumulative-dosing procedure, and the potency of DOM under these conditions was similar to its

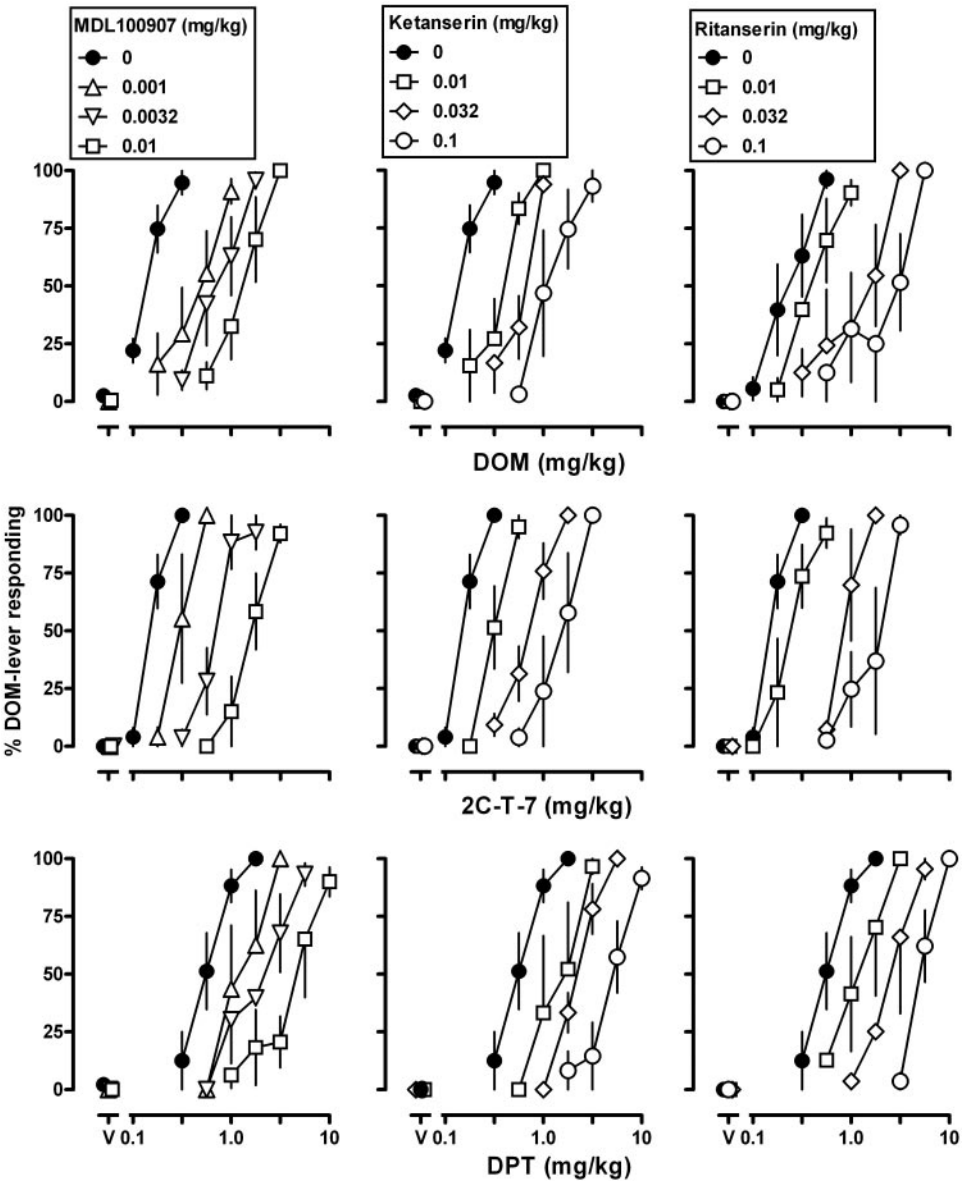

Fig. 2. Discriminative stimulus effects of DOM (top), 2C-T-7 (middle), and DPT (bottom) administered alone (filled symbols) and in combination with different doses of MDL100907 (left), ketanserin (center), and ritanserin (right). For other details, see Fig. 1.

potency determined when the same monkeys responded under a single-cycle, acute-dosing procedure (Li et al., 2008). Under this multiple-cycle, cumulative-dosing procedure, 2C-T-7 and DPT also increased responding on the DOM- associated lever, with potencies similar to their potencies under the single-cycle, acute-dosing procedure (Li et al., 2008). One general feature of drug discrimination procedures is pharmacological selectivity such that, in general, only drugs that share a mechanism of action with the training drug occasion responding on the drug-associated lever. In that regard, the apparent qualitative similarity in discriminative stimulus effects among these three compounds is consistent with actions at 5-HT_{2A} receptors. Although DPT also binds to 5-HT_{1A} receptors, and 2C-T-7 has similar affinity for 5-HT_{2A} and 5-HT_{2C} receptors (Fantegrossi et al., 2005), results of these substitution studies indicate that agonist activity at 5-HT_{2A} receptors accounts for the DOM-like discriminative stimulus effects of these drugs.

Drugs with affinity for and no apparent efficacy at 5-HT_{2A} receptors can attenuate the discriminative stimulus effects of DOM and related agonists in rats (Glennon et al., 1983) and in nonhuman primates (Li et al., 2008). Likewise, in the current study, drugs that are known to have antagonist actions at 5-HT_{2A} receptors antagonized the discriminative stimulus effects of all three 5-HT receptor agonists, in each case shifting the discrimination dose-response curve to the right. MDL100907 and ketanserin bind selectively to 5-HT_{2A} receptors, compared with 5-HT_{2C} receptors, whereas ritanserin has similar affinity for 5-HT_{2A} and 5-HT_{2C} receptors. Despite differences in their binding selectivity for different 5-HT receptors, all three antagonists blocked the effects of all three agonists in a dose-related and surmountable manner.

Schild analysis has been used to evaluate the behavioral effects of drugs acting at various different receptors, including opioid (Woods et al., 1988; France et al., 1990), $GABA_A$ (Paronis and Bergman, 1999), and 5-HT_{1A} receptors (Koek et al., 2000); however, this approach has not been used widely to examine the behavioral effects of drugs acting at 5-HT_{2A} receptors. Despite the challenges inherent with this analysis (e.g., Kenakin, 1982), particularly in vivo when assumptions

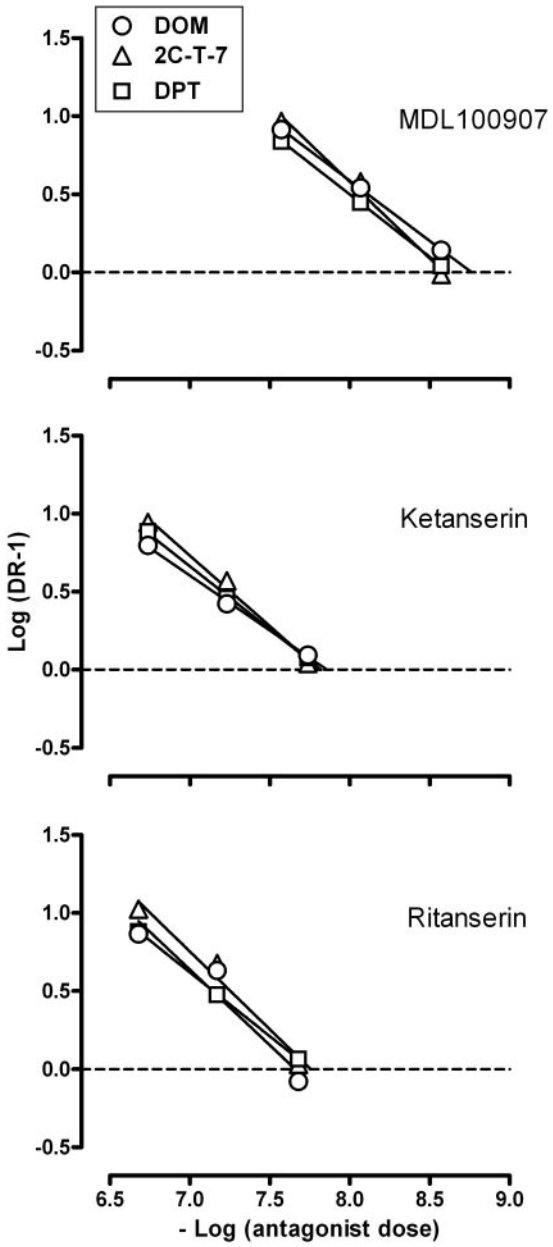

Fig. 3. Schild plots constructed from the same data shown in Fig. 2. Abscissa, negative log of the dose of antagonist in moles per kilogram of body weight. Ordinate, log of the dose ratio − 1.

(e.g., equilibrium) cannot be confirmed, it is noteworthy that orderly data can be obtained with this approach using behavioral data (Dykstra et al., 1988; Paronis and Bergman, 1999). Likewise, in the current study, the dose-response curves of each agonist were shifted to the right in an orderly dose-related manner by each of the antagonists. Moreover, for each drug combination, the Schild analysis yielded slopes that were not significantly different from unity (−1), a result that is consistent with a simple, competitive, and reversible interaction, probably at a single 5-HT receptor subtype (e.g., 5-HT_{2A}).

One value of Schild analysis is that the role of a particular receptor in the observed response can be confirmed quantitatively by comparing families of dose-response curves for combinations of agonists and antagonists that vary in selectivity for different receptors. Each of the agonists used in this study (DOM, 2C-T-7, and DPT) has activity at 5-HT_{2A} receptors, but each also has activity at other receptors. Likewise, each of the antagonists used in this study (MDL100907, ketanserin, and ritanserin) has affinity for 5-HT_{2A} receptors, but each also has affinity for other receptors. If only one receptor type mediates the effects of all drugs under a particular set of conditions, then under those conditions, the potency of an antagonist should be the same in blocking the actions of all agonists that have activity at that receptor. As shown by the convergence of regression lines on Schild plots (Fig. 3) and the estimated apparent pA_2 values (Table 1), the potency of each antagonist was remarkably similar with each of three different agonists. For example, the (unconstrained) apparent pA_2 values for ritanserin in combination with DOM, 2C-T-7, and DPT were 7.67, 7.76, and 7.76, respectively. Constraining the slope of the Schild plot to unity (−1) had little effect on the absolute value of the apparent pA_2 values or on the high degree of consistency among these values across agonists (Table 1), and this was the case for all three antagonists. Collectively, these results strongly suggest that a single receptor type mediates the effects of all three agonists and antagonists under these in vivo conditions and that the interaction of these drugs with that receptor type is simple, competitive, and reversible.

To the extent that only one receptor type mediates the effects of drugs under the conditions used in this discrimination study, the relative potency or affinity of these drugs for that receptor should predict their effects in this assay. That seems to be the case both for agonists and for antagonists. DOM and 2C-T-7 have similar potency, and both are 3-fold more potent than DPT in producing head twitching in mice (Fantegrossi et al., 2005, 2008b), an effect that is thought to be mediated by 5-HT_{2A} receptors. Based on apparent pA_2 values, ketanserin and ritanserin have very similar potency in antagonizing the discriminative stimulus effects of each agonist, being 10- to 17-fold less potent than MDL100907

TABLE 1
Results of Schild analyses for combinations of 5-HT_2 receptor antagonists and agonists in rhesus monkeys (n = 4)

Drugs	Slope (Unconstrained)	95% CL	pA_2 (Unconstrained)	95% CL	pA_2 (Constrained)	95% CL
MDL100907 and DOM	−0.77	(−0.53, −1.03)	8.77	(8.51, 9.03)	8.61	(8.46, 8.76)
MDL100907 and 2C-T-7	−0.98	(−0.60, −1.36)	8.59	(8.38, 8.80)	8.58	(8.44, 8.72)
MDL100907 and DPT	−0.80	(−0.36, −1.24)	8.62	(8.31, 8.94)	8.50	(8.33, 8.68)
Ketanserin and DOM	−0.70	(−0.33, −1.08)	7.86	(7.54, 8.01)	7.67	(7.51, 7.84)
Ketanserin and 2C-T-7	−0.90	(−0.53, −1.27)	7.81	(7.57, 8.05)	7.75	(7.61, 7.90)
Ketanserin and DPT	−0.81	(−0.45, −1.16)	7.78	(7.50, 8.06)	7.71	(7.57, 7.85)
Ritanserin and DOM	−0.97	(−0.61, −1.33)	7.67	(7.48, 7.86)	7.65	(7.52, 7.79)
Ritanserin and 2C-T-7	−1.00	(−0.65, −1.35)	7.76	(7.59, 7.92)	7.75	(7.63, 7.88)
Ritanserin and DPT	−0.81	(−0.38, −1.23)	7.76	(7.45, 8.07)	7.65	(7.48, 7.82)

TABLE 2
In vivo antagonism potencies and in vitro receptor binding affinities of MDL100907

	MDL100907	Ketanserin	Ritanserin
In vivo antagonism			
DOM discriminative stimulus (pA_2, mg/kg)	0.0006[a] (0.0003–0.0012)	0.0075[a] (0.0053–0.0157)	0.0102[a] (0.0071–0.0158)
(±)-1-(2,5-Dimethoxy-4-iodophenyl)-2-aminopropane -induced head twitch (ED_{50}, mg/kg)	0.005[b]	0.029[c] (0.009–0.096)	0.027[c] (0.008–0.091)
In vitro binding			
5-HT_{2A} receptor (K_i, nM)	0.85[d]	3.16[c]	3.80[c]
5-HT_{2C} receptor (K_i, nM)	88[d]	186[c]	2.3[c]
α_1 Adrenergic (K_i, nM)	128[d]	15[c]	190[c]

[a] Potency (milligrams per kilogram) to antagonize the DOM discriminative stimulus in monkeys (values in parentheses are the 95% confidence limits).
[b] ED_{50} recalculated from Vickers et al. (2001).
[c] From Kleven et al. (1997) (values in parentheses are 95% confidence limits).
[d] From Kehne et al. (1996).

in this regard. This potency relationship among these three antagonists parallels their relative potencies in blocking (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane-induced head twitching (Table 2). Moreover, the potency of MDL100907, ketanserin, and ritanserin in antagonizing the discriminative stimulus effects of DOM, 2C-T-7, and DPT parallels their relative binding affinities for 5-HT_{2A} receptors and not their relative binding affinities for 5-HT_{2C} or α_1 adrenergic receptors (Table 2). This striking similarity between antagonist potencies in the present study and receptor binding affinities in other studies provides strong evidence for these discriminative stimulus effects and, perhaps, the discriminative stimulus effects of other related drugs with hallucinogenic actions in humans being mediated by a single receptor type (5-HT_{2A}).

Acknowledgments

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