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The 5-HT_{1A} Receptor Agonist Flesinoxan Shares Discriminative Stimulus Properties With Some 5-HT_2 Receptor Antagonists

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HERREMANS, A. H. J., J. A. M. VAN DER HEYDEN, M. VAN DRIMMELEN AND B. OLIVIER. *The 5-HT_{1A} receptor agonist flesinoxan shares discriminative stimulus properties with some 5-HT_2 receptor antagonists.* PHARMACOL BIOCHEM BEHAV **64**(2) 389–395, 1999.—Ten homing pigeons were trained to discriminate the selective 5-HT_{1A} receptor agonist flesinoxan (0.25 mg/kg PO) from its vehicle in a fixed-ratio (FR) 30 two-key operant drug discrimination procedure. The 5-HT_2 receptor antagonist mianserin (ED_{50} = 4.8 mg/kg) fully substituted for flesinoxan, whereas ketanserin, ritanserin, mesulergine, and SB200646A substituted only partially, suggesting an interaction between 5-HT_{1A} and 5-HT_2 receptors. However, the 5-HT_2 receptor agonists [DOI (0.6 mg/kg), TFMPP (10 mg/kg), mCPP (4 mg/kg)] were unable to antagonize the flesinoxan cue. The 5-HT_{1A} receptor antagonists DU125530 (0.5–13 mg/kg) and WAY100,635 (0.1–1 mg/kg) partially antagonized the generalization of mianserin to flesinoxan. Taken together, these results are in accordance with the hypothesis that 5-HT_{1A} receptor activation exerts an inhibitory effect on activation of 5-HT_2 receptors. These results are in broad agreement with existing theories on 5-HT_{1A} and 5-HT_2 receptor interaction. Furthermore, it is argued that the discriminative stimulus properties of a drug may undergo qualitative changes with prolonged training. © 1999 Elsevier Science Inc.

Drug discrimination Discriminative stimulus Flesinoxan Mianserin 5-HT_{1A} receptor 5-HT_2 receptor Overshadowing Pigeons

SEROTONERGIC receptors, and especially the 5-HT_{1A} receptor subtype, have been suggested to play a role in anxiety and depression (8,9). Furthermore, it is well established that drugs with agonist actions at the 5-HT_{1A} receptor are active in animal models of anxiety (3,7). The 5-HT_{1A} receptor is, therefore, considered a target for possible therapeutic drugs, and several 5-HT_{1A} receptor agonists are currently in development.

One such compound is flesinoxan, a potent and selective 5-HT_{1A} receptor agonist (K_i = 1.7 nM), with anxiolytic-like effects in several preclinical models [e.g., stress-induced hyperthermia (27), ultrasonic vocalization (15), Geller-Seifter Conflict procedure in both pigeons (3), and rats (14)].

Drug discrimination studies in the rat have shown that the discriminative stimulus properties of flesinoxan are exclusively mediated by the 5-HT_{1A} receptor (10,22,25,26). Recently, drug discrimination experiments in pigeons trained to discriminate flesinoxan from vehicle have confirmed that, also in this species, the discriminative stimulus properties of flesinoxan are mediated by the 5-HT_{1A} receptor (16).

Evidence exists for an interaction between the 5-HT_{1A} and 5-HT_2 receptors (4,5). Blockade of 5-HT_2 receptors has been shown to enhance 5-HT_{1A} receptor-mediated effects. For example, the 5-HT_2 receptor antagonists metergoline, ritanserin, and ketanserin potentiate 8-OH-DPAT-induced hypothermia (1,11,12). Moreover, it has been shown that the 5-HT_{1A} receptor agonist 8-OH-DPAT antagonizes DOI (a 5-$HT_{2A/C}$ receptor agonist)-induced wet dog shakes (WDS), while the 5-HT_{1A} receptor antagonist WAY100,635 potentiates the induction of WDS by DOI (21).

Taken together, these results constitute evidence for interactions between 5-HT_{1A} and 5-HT_2 receptors. The exact nature of these interactions, however, remains unclear. The present study investigated whether the discriminative stimulus properties of the 5-HT_{1A} receptor agonist flesinoxan in the

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pigeon show an interaction with compounds acting at the 5-HT_2 receptor as well. Generalization and antagonism studies with 5-HT_2 receptor antagonists were, therefore, conducted in pigeons trained to discriminate flesinoxan from vehicle. The results indicate that 5-HT_2 receptor antagonists and flesinoxan may have stimulus properties in common.

METHOD

Subjects

Ten homing pigeons, obtained from Utrecht University, Department of Veterinary Sciences, served as subjects. After having been trained to discriminate flesinoxan from vehicle (16), they had been used for 6 years in drug discrimination experiments. They were approximately 6 years old at the start of the present experiments.

Throughout the experiment the pigeons were kept at approximately 85% of their free-feeding body weights by means of postsession supplemental feeding with standard pigeon grain. Animals were housed individually from 0800–1400 h, during which the experiments were conducted, and were house in groups at all other times. Water and grit were continuously available.

Apparatus

Eight standard Lehigh Valley three-key pigeon chambers were used. Only the left and the right key were operative during the experiment. The keys (2.5 cm in diameter) were located 9 cm from the right and left hand walls, spaced 16.5 cm apart (center to center), and mounted 23 cm from the floor of the chamber. One key was illuminated by a green light, and the other by a red light. They required a force of approximately 0.15 N to be operated. Access to mixed pigeon grain was provided through a 5 × 6 cm aperture, centered on the intelligence panel 11 cm from the floor of the chamber. All chambers were enclosed in a sound-attenuated cabinet; a fan provided fresh air and masking noise. The chambers were connected to a Vectra ES/12 personal computer (Hewlett Packard) located in the same room. Experimental contingencies and data acquisition were programmed using MED-PC (19).

PROCEDURES

Drug Discrimination Training

Subjects were already trained to discriminate flesinoxan from vehicle [see (15) for full description]. In brief, training went as follows. Subjects were trained to peck a key and, subsequently, to emit responses on a fixed ratio 30 (FR30) schedule of reinforcement (4-s access to mixed grain, maximum 45 reinforcements per 30-min session). During discrimination training 0.25 mg/kg flesinoxan or vehicle were administered PO 45 minutes before each session, according to a 10-days repeating ABAAB BABBA drug-vehicle design. On flesinoxan days, responding on the red key was reinforced according to an FR30 schedule, and on vehicle days, responding on the green key was reinforced according to an FR30 schedule. The position of the red and green key varied across subjects.

The first reinforcement (FRF) value was defined as the total number of responses on both keys until the first reinforcement was delivered. Subjects were considered to have selected the correct key when the FRF value did not exceed 39 (e.g., no more than nine responses on the incorrect key). A 5-s time out (all stimulus lights and houselight turned off) occurred when more than 90 responses were recorded before the presentation of the first reinforcer. This time out also occurred after each response on the incorrect key after subjects had received the first reinforcement. Training continued until a subject had selected the correct key on at least 8 out of 10 consecutive training sessions. Sessions lasted 20 min or until subjects had earned 40 reinforcements, whichever came first. Training sessions were conducted 5 days a week, Monday through Friday.

Test Sessions

When training criterion was attained, test sessions were interspersed between training sessions. The key on which the first 30 responses had accumulated was designated the to-be-rewarded key for each individual subject for the rest of that particular test session. A 5-s time out occurred after each response on the nonselected key after the presentation of the first reinforcement. Test sessions ended after 20 min or 40 reinforcements, whichever came first. Test sessions were held on Tuesday and Friday, but only if the subject's FRF value on the three immediately preceding training sessions did not exceed 39. In the latter case, the test session was postponed until the next test day.

Data Analysis

The percentage of subjects selecting the key associated with the administration of flesinoxan was taken as a measure of generalization. Generalization or substitution was said to occur when at least 80% of all subjects selected the flesinoxan-associated key. Antagonism of the flesinoxan cue was defined as at most 20% of all subjects showing flesinoxan-appropriate responding at doses of flesinoxan, that when given alone produced at least 80% drug-appropriate responding. ED_{50} values with 95% confidence limits were calculated by means of log-probit analysis.

Response rates were calculated as the number of key pecks per second until the delivery of the first reinforcement. Even when this rate was not affected, some animals stopped responding during the remainder of the test session. This was taken to indicate that higher doses could not be tested. Control values were obtained from the response rates during the last three training sessions. Differences between control values and response rates on test sessions were analyzed by means of Student's *t*-test, two-tailed test of significance.

Drugs

Drugs were suspended in methylcellulose (1.25% w/v) and administered orally (PO) into the crop in a volume of 1 ml/kg. The following drugs were tested: flesinoxan, DU125530 {2-[4-[4-(7-chloro-2,3-dihydro-1,4-benzodioxin-5-yl)-1-piperazinyl]butyl]-1,2-benzisothiazol-3(2H)-one-1,1-dioxide}, WAY100635 HCl (N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridinyl)cyclo-hexane-carboxamide, (all synthesized by the department of Medicinal Chemistry, Solvay-Pharmaceuticals, Weesp, The Netherlands); mianserin (1,2,3,4,10,14b-hexahydro-2-methyldibenzo[c,f]pyryzinol[1,2-a]azepine hydrochloride), ketanserin (3-[2-[4-(4-fluorobenzoyl)-1-piperdinyl]ethyl]-2,4 (1H, 3H)-quinazolinedione tartrate), ritanserin (6-[2-[4-[*bis*(4-fluorophenyl)methylene]-1-piperdinyl]-ethyl]-7-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one), mesulergine, TFMPP (N-(3-trifluormethylphenyl)piperazine hydrochloride), DOI (±-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane hydrochloride), and mCPP (1-(3-chlorophenyl)-piperazine dihydrochloride) purchased from Research Biochemical International, Germany and

SB200646A (n-(1-methyl-5-indolyl)-n-(3-pyridyl)yrea) kindly donated by Smith Kline Beecham.

Flesinoxan (0.25 mg/kg) as well as all other drugs used for generalization studies were administered 45 min before the session. In antagonism studies, the antagonist was administered 15 min before the agonist, and 60 min before the session. All doses of a particular compound were tested, in a random order, in the same subjects.

EXPERIMENT I

In Experiment I, various doses of flesinoxan (0.01–1 mg/kg) were tested, and the ability of the following 5-HT$_2$ receptor antagonists to produce flesinoxan-appropriate responding was examined: mianserin (0.3–30 mg/kg), ketanserin (1–30 mg/kg), ritanserin (1–30 mg/kg), mesulergine (0.125–4 mg/kg), and SB200646A (1–30 mg/kg).

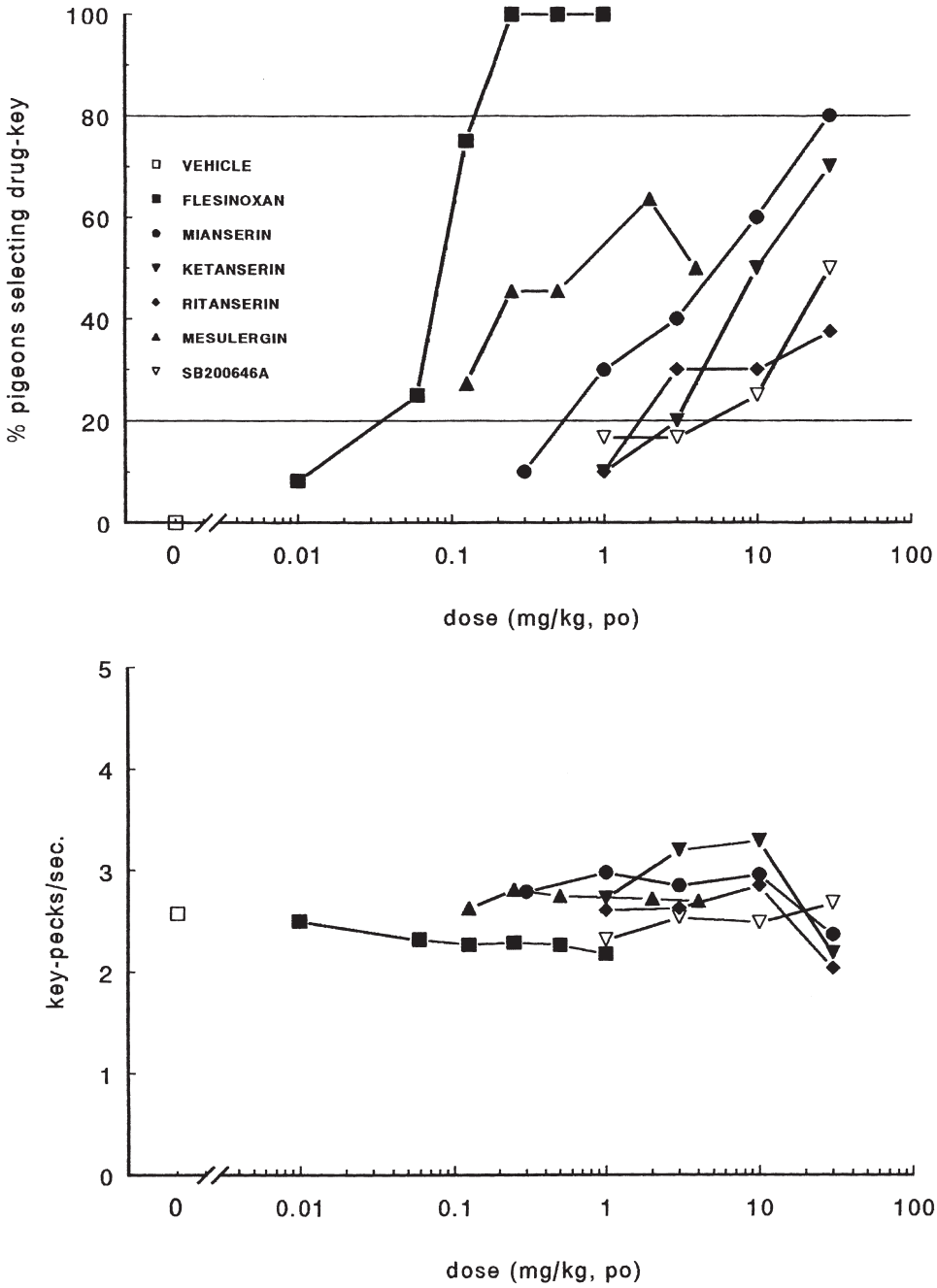

FIG. 1. Results of substitution studies in pigeons trained to discriminate 0.25 mg/kg flesinoxan from saline. The upper part shows the percentage of pigeons selecting the drug key as a function of increasing doses of the tested compounds. The numbers of pigeons that completed the whole dose range are: ketanserin [10], mianserin [10], ritanserin [8], mesulergine [10], and SB200646A [10]. The lower part shows corresponding response rates (key pecks per second).

Results

Flesinoxan dose dependently induced selection of the flesinoxan-appropriate key with an ED_{50} of 0.09 mg/kg PO (conf. limits 0.06–0.12 mg/kg). Mianserin substituted for flexinoxan (ED_{50} = 4.8 mg/kg; conf. limits 1.7–18.0 mg/kg), whereas ketanserin (>30 mg/kg), mesulergine (>4 mg/kg), SB200646A (>30 mg/kg), and ritanserin (>30 mg/kg) only partially generalized to flesinoxan (Fig. 1). Response rates were not significantly affected by any of the drugs tested.

Discussion

The dose–response curve of flesinoxan observed here is very similar to that obtained previously in these same animals (16), suggesting that tolerance or sensitization to the discrimi-

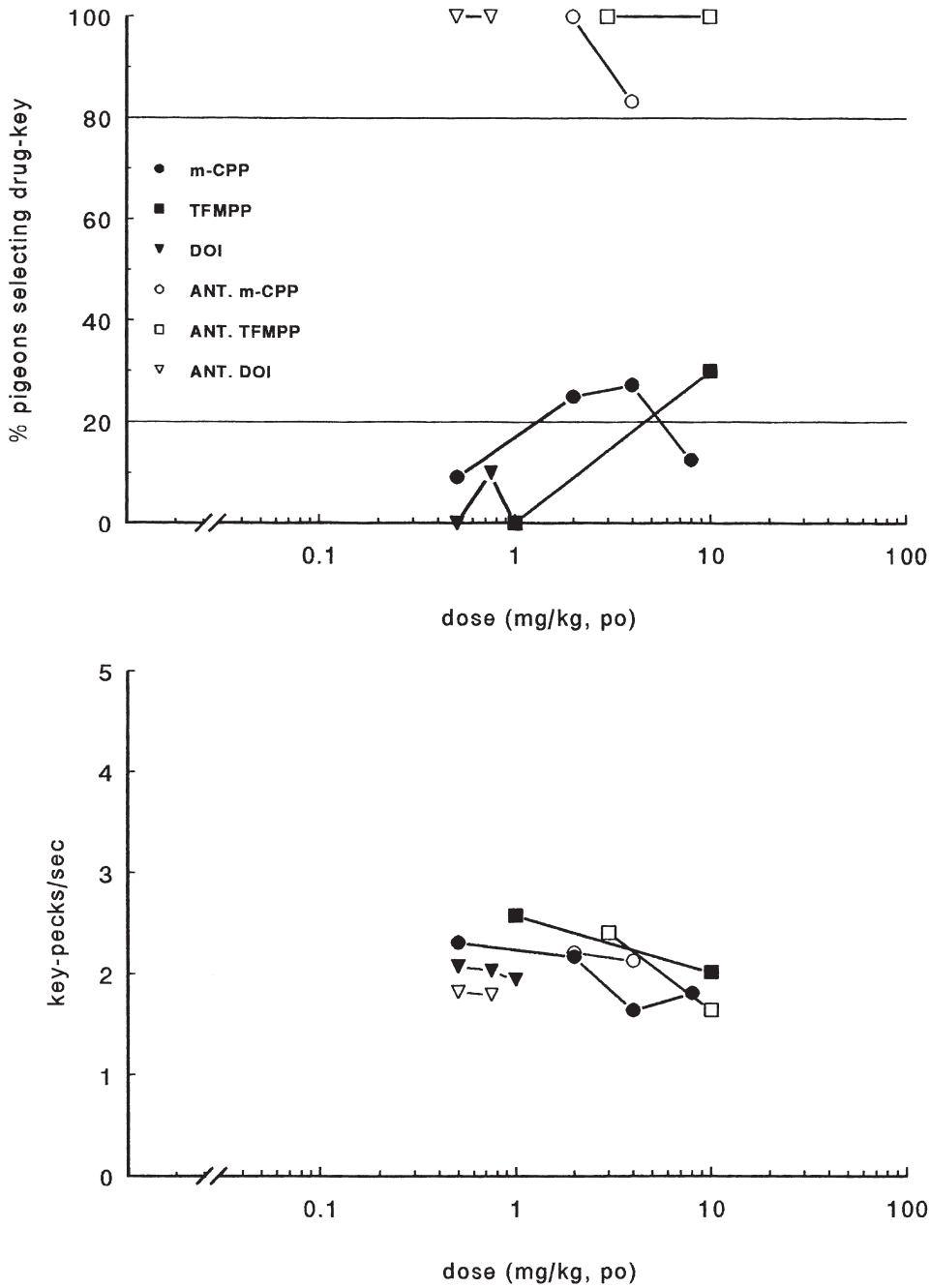

FIG. 2. Results of substitution (filled symbols) and antagonism (open symbols) studies in pigeons trained to discriminate 0.25 mg/kg flesinoxan from saline. The upper part shows the percentage of pigeons selecting the drug key. The numbers of pigeons that completed the whole dose range are: DOI [3], TFMPP [8], and mCPP [8]. The lower part shows corresponding response rates (key pecks per second).

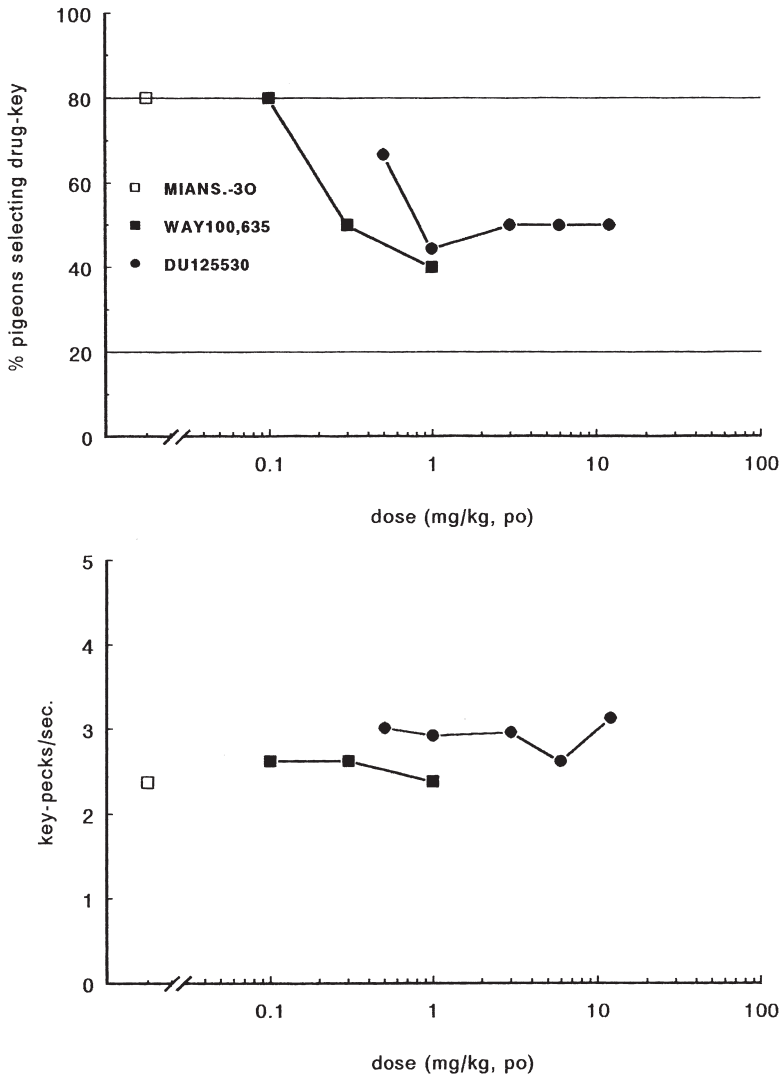

FIG. 3. Results of antagonism of mianserin induced drug key responding in pigeons trained to discriminate 0.25 mg/kg flesinoxan from saline. The upper part shows the percentage of pigeons selecting the drug key after antagonism of mianserin was carried out with DU125530 [10] and WAY100,635 [10]. The lower part shows corresponding response rates (key pecks per second).

native stimulus properties of flesinoxan did not develop over a 6-year training period.

Experiment I investigated a possible role of 5-HT$_2$ receptors in the discriminative stimulus properties of the 5-HT$_{1A}$ receptor agonist flesinoxan, by examining the ability of several 5-HT$_2$ receptor antagonists to produce flesinoxan-appropriate responding. Mianserin substituted for flexinoxan, while ketanserin, ritanserin, mesulergine, and SB200646A substituted only partially. These results suggest that 5-HT$_2$ receptor antagonists, mianserin in particular, and flesinoxan may share some discriminative stimulus properties in the pigeon. Because these drugs lack affinity for the 5-HT$_{1A}$ receptor (20), their ability to produce flesinoxan-appropriate responding is unlikely to involve 5-HT$_{1A}$ receptors, but may constitute further evidence of functional interactions between 5-HT$_{1A}$ and 5-HT$_2$ receptors.

5-HT$_{1A}$ receptors are located pre- and postsynaptically, whereas 5-HT$_2$ receptors are located only postsynaptically (17). Thus, it is plausible that the interaction between both receptors occurs at the postsynaptic level. It has been suggested that 5-HT$_2$ receptors exert inhibitory control over the 5-HT$_{1A}$ receptor through a tonic presence of endogenous serotonin (2). Release of this inhibition, by a 5-HT$_2$ receptor antagonist can, therefore, result in 5-HT$_{1A}$ receptor agonist-like effects induced by endogenous serotonin acting at 5-HT$_{1A}$ receptors; hence, generalization of 5-HT$_2$ receptor antagonists to flesinoxan. This hypothesis generates the following predictions. First, if 5-HT$_2$ receptors tonically inhibit 5-HT$_{1A}$ receptors, increasing this inhibitory action by administration of a 5-HT$_2$ receptor agonist should antagonize the discriminative stimulus effects of flexinoxan. Second, a 5-HT$_{1A}$ receptor antagonist will reduce the endogenous activity at the 5-HT$_{1A}$ receptor, and should, therefore, counteract the disinhibition of 5-HT$_{1A}$ receptors caused by a 5-HT$_2$ receptor antagonist. Thus, a 5-HT$_{1A}$ receptor antagonist should counteract the generalization to flesinoxan of a 5-HT$_2$ receptor antagonist (e.g., mi-

anserin). It was the aim of Experiment II to examine these predictions.

EXPERIMENT II

First, we studied whether 5-HT_2 receptor agonists [DOI (0.5–1 mg/kg), TFMPP (1–10 mg/kg), and mCPP (0.5–7.5 mg/kg)] would antagonize the flesinoxan cue. Second, we examined whether 5-HT_{1A} receptor antagonists [DU125530 (0.5–12 mg/kg) and WAY100,635 (0.1–1 mg/kg)] were able to antagonize flexinoxan appropriate responding by mianserin (30 mg/kg). All compounds were tested for their ability to generalize to flesinoxan as well.

Results

Figure 2 shows the results of the antagonism tests with mCPP, TFMPP, and DOI; clearly, none of these drugs antagonized the discriminative stimulus effects of flesinoxan (0.25 mg/kg). Further, when given alone, mCPP (0.5–10 mg/kg), TFMPP (0.5–10 mg/kg), and DOI (0.5–1.0 mg/kg) failed to generalize to flesinoxan. Figure 3 shows that the generalization of mianserin (30 mg/kg) to flesinoxan was antagonized only partially by DU125530 (45% drug key selection at 1.0 mg/kg) and WAY100,635 (50% drug key selection at 0.3 mg/kg).

Discussion

The results of Experiment II show that 5-HT_2 receptor agonists were not able to antagonize the flesinoxan cue. This suggests that the putative inhibitory action of 5-HT_2 receptors on the 5-HT_{1A} receptor was not increased by administration of a 5-HT_2 receptor agonist, at least not to such an extent that it disrupted the 5-HT_{1A} receptor-mediated discriminative stimulus effects of flexinoxan.

Experiment II also showed that 5-HT_{1A} receptor antagonists partially antagonized the mianserin-induced generalization to flesinoxan. This suggests that the 5-HT_{1A} receptor plays a role in the generalization of mianserin to flesinoxan. Given the low affinity of mianserin for the 5-HT_{1A} receptor (Table 1), the generalization of mianserin to flesinoxan is unlikely to be mediated by direct 5-HT_{1A} agonist properties of mianserin, but may involve indirect 5-HT_{1A} agonist actions.

In rats, it has been shown that wet dog shakes (WDS), induced by the 5-$HT_{2A/C}$ receptor agonist DOI, is inhibited by 5-HT_{1A} receptor agonists (21), suggesting that 5-HT_{1A} receptor activation functionally inhibits 5-HT_2 receptor-mediated effects [see also (6)]. In the present experiment, pigeons have learned to recognize a 5-HT_{1A} receptor agonist-induced cue. The generalization of a 5-HT_2 receptor antagonist (mianserin) to flesinoxan indicates that part of the flesinoxan cue resembles inhibition of 5-HT_2 receptors. This suggests that, analogue to the results obtained from the WDS model in rats, in the pigeon 5-HT_{1A} receptor stimulation functionally inhibits 5-HT_2 receptors, as well.

Only one of the five 5-$HT_{2A/2C}$ receptor antagonist that were tested showed full generalization to flesinoxan. From Table 1 it can be seen that the affinity for the D_2 receptor is lowest for mianserin and highest for ritanserin, the compounds with the highest and the lowest amount of generalization, respectively, suggesting an inverse relation between the amount of generalization and the affinity for the D_2 receptor. The higher the affinity for the D_2 receptor, the lower the amount of generalization. This suggests an even more complex interaction between 5-HT_{1A} receptors, D_2 receptors, and 5-HT_{1A} receptors. Although serotonergic and dopaminergic interaction have been reported frequently (13), the present data do not warrant further speculation on the exact nature of these interactions.

TABLE 1

AFFINITIES (pK_i–VALUES FOR SOME SEROTONERGIC AND DOPAMINERGIC RECEPTOR SUBTYPES OF THE COMPOUNDS TESTED

Compound	5-HT_{1A}	5-HT_{2A}	5-HT_{2C}	α_1	D_1	D_2
Flesinoxan	8.8	5.4	4.9	6.4	4.7	6.9
Mianserin	6.1	8.0	9.0	7.1	5.9	6.0
Ketanserin	6.2	8.7	7.4	8.1	5.1	6.5
Mesulergin	6.8	7.6	8.6	5.8	nt	7.8
SB200646A	4.4	4.5	6.2	nt	nt	nt
Ritanserin	6.1	8.5	9.6	7.1	6.2	7.9
DOI	5.2	6.7	7.8	5.1	5.2	5.5
TFMPP	6.7	6.1	7.5	5.9	5.1	6.1
mCPP	6.7	6.3	7.3	6.4	5.0	5.6
WAY100635	9.3	5.7	5.5	6.9	4.7	7.1
DU125530	9.1	6.5	6.4	8.2	<5.1	8.3

n.t.—not tested.

The result of Experiment II shows that a 5-HT_{1A} receptor antagonist can partially antagonize mianserin-induced responding on the drug key. This result may be explained in two ways. First, a 5-HT_{1A} receptor antagonist may reduce the 5-HT_{1A} receptor-mediated inhibition of 5-HT_2 receptors, therefore shifting the mianserin dose–response curve to the right; hence, partial antagonism of mianserin. Second, Table 1 shows that both 5-HT_{1A} receptor antagonists possess considerable affinity for the D_2 receptor. According to the suggested inverse relation between D_2 receptor affinity and the amount of generalization to flesinoxan of the 5-HT_2 receptor antagonists, D_2 receptor-mediated effects of both 5-HT_{1A} receptor antagonists may have disrupted the generalization of mianserin. Further experiments are needed to elucidate the putative role of D_2 receptors in these experiments.

Experiments with rats trained to discriminate 5-HT_{1A} receptor agonists from vehicle have thus far been unable to show such 5-HT_{1A}–5-HT_2 receptor interactions (23,24). Why pigeons are able to show this interaction in a drug discrimination experiment may be related to a species difference. Another cause for the difference between drug discrimination research in the rat vs. the pigeon may be related to the fact that pigeons can be used for a considerable longer period of time than rats. During that longer training period the discriminative stimulus properties may have become more sophisticated by slowly incorporating more subtle aspects of the discriminative stimulus. For example, interactions with other receptors (e.g., inhibition of 5-HT_2 receptors) may initially have been overshadowed by the main stimulus properties (e.g., 5-HT_{1A} receptor agonism), but may have gained associative strength, and therefore, stimulus control, with prolonged (6 years) training (18). This predicts that at the start of testing, 6 years ago, mianserin would not have generalized to flesinoxan in these pigeons, which was regrettably not tested back then.

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