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European Journal of Pharmacology 284 (1995) 135–140

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Discriminative stimulus properties of flesinoxan: effects of enantiomers, (*S*)-UH301 and WAY-100635

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Received 2 February 1995; revised 13 June 1995; accepted 23 June 1995

Abstract

Rats were trained to discriminate the specific 5-HT_{1A} receptor agonist (+)-flesinoxan (*R*(+)-*N*-[2[4-(2,3-dihydro-2-2-hydroxymethyl-1,4-benzodioxin-5-yl)-1-piperazinyl]ethyl]-4-fluorobenzoamide) (1.5 mg/kg p.o.) from water in a two-lever operant procedure. Generalization tests were conducted with the enantiomers and racemate of flesinoxan and the 5-HT_{1A} receptor antagonists (*S*)-UH301 ((*S*)-5-fluoro-8-hydroxy-2-(dipropylamino)-tetralin) and WAY-100635 ((*N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-(2-pyridinyl) cyclohexanecarboxamide trihydrochloride). (*S*)-UH301, WAY-100635 and fentanyl were investigated for their antagonistic properties. The (+)-flesinoxan stimulus generalized to (−)-flesinoxan and the racemate. The ED_{50} values for generalization corresponded well with the affinities of the enantiomers and the racemate for the 5-HT_{1A} receptor. The flesinoxan cue could not be mimicked by (*S*)-UH301 or WAY-100635, but (*S*)-UH301 reduced response rates. Antagonism tests showed that both (*S*)-UH301 and WAY-100635 dose dependently antagonized the flesinoxan cue, with ID_{50} values of 0.52 and 0.03 mg/kg s.c., respectively. Fentanyl had no significant antagonistic properties. It is concluded that rats can learn to discriminate orally administered (+)-flesinoxan from water. The generalization of flesinoxan to the (−)-enantiomer and the antagonism of flesinoxan's cue by specific 5-HT_{1A} receptor antagonists are further evidence for the involvement of flesinoxan's 5-HT_{1A} receptor agonistic properties in its discriminative stimulus effects.

Keywords: Flesinoxan; Drug discrimination; 5-HT_{1A} receptor; (*S*)-UH301, enantiomer; WAY-100635; Fentanyl

1. Introduction

The phenylpiperazine derivative flesinoxan (*R*(+)-*N*-[2[4-(2,3-dihydro-2-2-hydroxymethyl-1,4-benzodioxin-5-yl)-1-piperazinyl]ethyl]-4-fluorobenzoamide) is currently under investigation for its anti-anxiety and anti-depressive properties in humans (Bradford, 1993; Grof et al., 1993) and is active in animal models predictive for anxiety and depression (Olivier et al., 1994; Schipper et al., 1991). Flesinoxan binds with high affinity and selectivity to central 5-HT_{1A} receptors (Wouters et al., 1989). Results of drug discrimination studies with flesinoxan are in agreement with a 5-HT_{1A} mechanism of action. Flesinoxan generalized to the 5-HT_{1A} receptor agonists 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT), gepirone, and ipsapirone could be blocked with the 5-HT_{1A}/β-adrenoceptor antagonist pindolol but not with specific dopaminergic receptor or adrenoceptor antagonists prazosin, haloperidol, pimozide and idazoxan (Ybema et al., 1990, 1991, 1993, 1994a,b). Most investigations use the (+)-enantiomer of flesinoxan which has a higher affinity for the 5-HT_{1A} receptor than the (−)-enantiomer or its racemate (K_i = 1.7 nM, 15 nM and 4.7 nM, respectively) (Tulp, personal communication). The purpose of the present experiment was to investigate, using a drug discrimination procedure, whether (−)-flesinoxan and its racemate induce a 5-HT_{1A} 'cue' in animals trained to discriminate (+)-flesinoxan from vehicle.

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Elsevier Science B.V.
SSDI 0014-2999(95)00391-6

Until recently, the only 5-HT_{1A} receptor antagonists available were non-specific receptor antagonists like the β-adrenoceptor/5-$HT_{1A/B}$ receptor antagonists pindolol, alprenolol, propranolol and cyanopindolol (Middlemiss et al., 1977; Nahorski and Willcocks, 1983; Tricklebank, 1985; Tricklebank et al., 1987; Zifa and Fillion, 1992) and the α_1-adrenoceptor/5-HT_{1A} receptor antagonist NAN-190 (Glennon et al., 1989). Some of the compounds reported to be antagonists were found to be partial agonists (Fletcher et al., 1993). These compounds are able to (partially) antagonize the stimulus properties of 5-HT_{1A} receptor agonists (Barret and Gleeson, 1992; Tricklebank et al., 1987; Ybema et al., 1993,1994a). Recently (*S*)-UH301 ((*S*)-5-fluoro-8-hydroxy-2-(dipropylamino)-tetralin) and WAY-100635 (*N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-(2-pyridinyl) cyclohexanecarboxamide trihydrochloride) have been reported to be silent 5-HT_{1A} receptor antagonists (Björk et al., 1991; Fletcher et al., 1994; Gurling et al., 1994; Hartley et al., 1994). It is investigated in the present study whether (*S*)-UH301 and WAY-100635 have 5-HT_{1A} receptor agonistic properties and if they can antagonize the stimulus cue of flesinoxan.

Interestingly, there are interactions between opioid narcotics and the serotonergic system. It is reported that fentanyl and sufentanil inhibit binding of [^{3}H]8-OH-DPAT to hippocampal membranes (Martin et al., 1991). The serotonergic system is also involved in the discriminative stimulus effects of morphine and U50,488 (Powell et al., 1994). These last authors were able to show that the discriminative stimulus properties of 8-OH-DPAT can be antagonized with morphine and fentanyl. We therefore investigated the antagonistic activity of fentanyl in flesinoxan-trained subjects.

In most drug discrimination studies compounds are administered intraperitoneally or subcutaneously. However, because therapeutic drugs are most often administered orally, this route of administration was preferred in the present study.

2. Materials and methods

2.1. Subjects

Eight male Wistar rats, weighing approximately 300 g at the start of the training, were obtained from GDL (Utrecht, Netherlands). One animal died during the course of the experiment, the cause of death being unrelated to the experimental conditions. Rats were housed individually under a non-reversed 12 h light-dark cycle and a room temperature of 21–23°C. Tap water was freely available. Subjects were maintained at approximately 85% of their expected free-feeding weight by providing them with a diet of 14 g food (Hope Farms) 1 h after each daily session (Monday to Thursday). On Friday afternoon they received 50 g food for the whole weekend.

2.2. Apparatus

Eight ventilated operant chambers (MED Associates, East Fairfield, UK) equipped with two levers and housed in sound-insulated boxes were used. A pellet dispenser delivered 45 mg pellets (Noyes Company, Lancaster, New Hampshire, UK) in a tray placed between the levers. An IBM personal computer using an MED interface with software controlled experimental sessions and recorded data.

2.3. Training procedure

After initial lever-press training, the rats were trained to lever-press according to a fixed ratio 10 (FR 10) schedule of reinforcement. Thereafter rats were trained to discriminate (+)-flesinoxan (1.5 mg/kg) from deionized water. Initially animals were trained with a dose of 1.0 mg/kg, but because of a low stimulus control the dose was increased to 1.5 mg/kg. Depending on the injection conditions, reinforcement could be obtained by pressing ten consecutive times either on the drug-appropriate or the water-appropriate lever. Responding on the inappropriate lever reset the counter for the appropriate lever. The position of the drug (D) and water (W) levers was counterbalanced across rats. Forty-five minutes before the daily sessions the animals were injected with either drug or water, according to a 2-weekly alternating schedule (D-W-D-D-W, W-D-W-W-D). For half the animals the discrimination training started with the first half of the sequence, for the other half training started with the second part. Drug-induced stimulus control was assumed to be present when the animal accurately selected the appropriate lever within ten consecutive sessions (5 D and 5 W). The lever on which the rat first made ten consecutive responses was scored as the selected lever. Accurate lever selection was defined as selection of the appropriate lever with three or fewer responses on the inappropriate lever.

2.4. Testing procedure

Generalization and antagonism tests were carried out on Wednesday and Friday. On the remaining days the training procedure was continued. Throughout the test session, responding on the selected lever was rewarded according to a FR 10 schedule. The test sessions ended after 15 min or when the animal had obtained 30 reinforcements. Stimulus generalization was defined in two ways: (1) after receiving a dose of the test compound, at least 80% of the animals se-

lected the drug-appropriate lever; (2) before obtaining the first reinforcement, 80% of the responses or more were made on the drug-appropriate lever. Stimulus antagonism was defined in a similar manner: (1) after receiving a dose of the test compound in combination with flesinoxan, 20% or fewer of the animals selected the drug-appropriate lever; (2) before obtaining the first reinforcement 20% of the responses or fewer were made on the drug-appropriate lever. The sequence in which different drugs were tested was the same for all rats. Flesinoxan was administered orally 45 min before the test, (*S*)-UH301, WAY-100635 and fentanyl were administered subcutaneously 30 min before the test.

2.5. Data analysis

Generalization and antagonism test results are expressed as the percentage of animals selecting the drug appropriate lever (quantal measurement) and as the mean percentage drug-lever responding before delivery of the first reinforcement (quantitative measurement). As suggested by Zenich and Greene (1978) quantitative generalization data were analyzed by means of Friedman's analysis of k related samples or Wilcoxon's analysis for 2 related samples using the statistical package of SPSS-pc. Generalization data were analyzed with inclusion of the water condition, antagonism with the 1.5 mg/kg flesinoxan condition. Using quantitative data, a curve fit was computed by linear regression which provided an ED_{50} for generalization and an ID_{50} for antagonism. Response rates were analyzed by means of analysis of variance with repeated measures on drug dose (having between two and six levels). The MANOVA statistical package of SPSS-pc was used. A significance level of 5% was chosen for all effects.

2.6. Drugs

(+)-Flesinoxan-HCl, (−)-flesinoxan-HCl and the racemate (Solvay Duphar, Weesp, Netherlands) were dissolved in demineralized water. (*S*)-UH301 and WAY-100635 (synthesized by Solvay Duphar) were dissolved in 0.9% NaCl. All solutions were prepared fresh daily. Flesinoxan was administered orally, (*S*)-UH301 and WAY-100635 subcutaneously, all in a volume of 2 ml/kg body weight. The standard solution fentanyl citrate (0.05 mg/ml) as delivered by the supplier (Janssen Pharmaceutica, Beerse, Belgium) was used and injections were made subcutaneously.

3. Results

3.1. Discrimination training

All rats learned to discriminate flesinoxan from water. Initially they were trained with 1 mg/kg p.o. (average number of sessions to criterion: 77, range: 39–114). Because accurate performance during subsequent training sessions was still somewhat unstable, the animals were trained additionally with 1.5 mg/kg for 20 sessions. After this performance remained stable and testing was started.

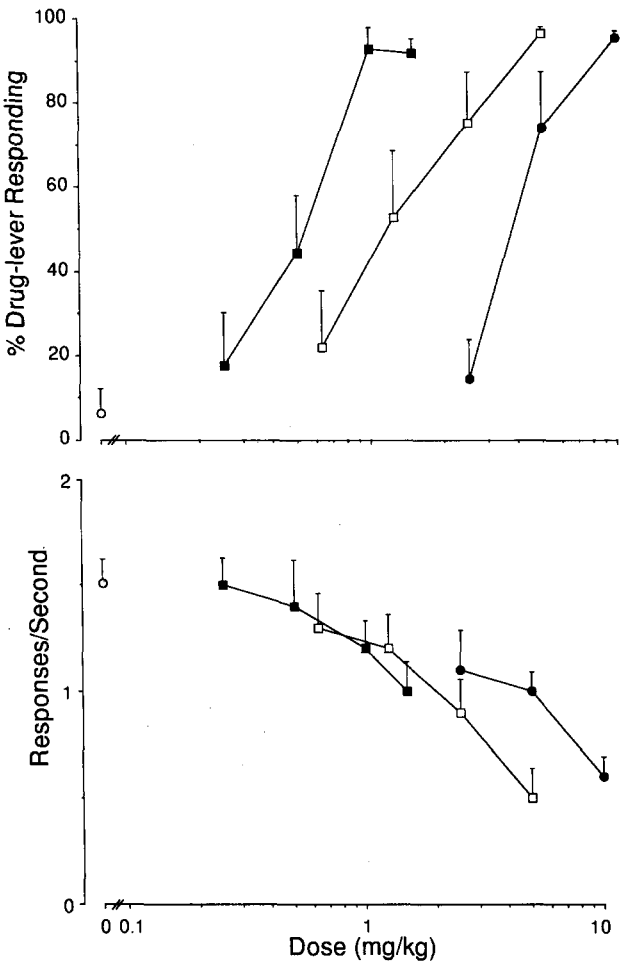

Fig. 1. Results of substitution tests with (+)-flesinoxan (■), (−)-flesinoxan (●), its racemate (□) and water (○) in rats trained to discriminate 1.5 mg/kg (+)-flesinoxan from water. Ordinate upper panel: mean percentage of responses on the (+)-flesinoxan appropriate lever (±S.E.M.). Ordinate lower panel: response rate (responses/second) (±S.E.M.). Abscissa: dose plotted on a log scale.

3.2. Effects of enantiomers

Fig. 1 shows the results of tests with different enantiomers of flesinoxan. The enantiomer and the racemate generalized completely to the (+)-flesinoxan stimulus ((+)-flesinoxan $\chi^2(4) = 21.1$, $P < 0.05$; (−)-flesinoxan $\chi^2(3) = 15.3$, $P < 0.05$; racemate $\chi^2(4) = 17.3$, $P < 0.05$). Both quantal (not shown) and quantitative measurements yielded the same results. (−)-Flesinoxan was the least potent. The ED_{50} values were: (+)-flesinoxan 0.57 mg/kg; (−)-flesinoxan 4.7 mg/kg;

racemate 1.6 mg/kg. The MANOVA showed an effect on response rates by (−)-flesinoxan ($F(3,3) = 16.57$, $P < 0.05$) but not by (+)-flesinoxan or the racemate ($F(4,3) = 1.64$, $P > 0.05$ and $F(4,3) = 6.12$, $P > 0.05$ respectively).

3.3. Effects of subcutaneous saline injections

Saline injections alone did not induce drug-lever responding ($Z = -0.7$, $P > 0.05$) or alter response rates ($F(1,6) = 0.13$, $P > 0.05$) and when administered together with flesinoxan it did not reduce drug-lever responding ($Z = -0.4$, $P > 0.05$) but had an effect on response rates ($F(1,6) = 8.72$, $P < 0.05$) (Table 1).

3.4. Effects of (S)-UH301, WAY-100635 and fentanyl

Because saline injections did not alter drug-lever responding, these data were used to analyse all subsequent experiments with subcutaneous drug administration.

When administered alone (*S*)-UH301 did not induce significant drug-lever responding ($Z = -0.5$, $P > 0.05$) (Table 1). (*S*)-UH301 reduced response rates ($F(1,6) = 62.53$, $P < 0.05$). When administered together with the training dose of flesinoxan (1.5 mg/kg), (*S*)-UH301 dose dependently antagonized the flesinoxan stimulus ($\chi^2(5) = 24.0$, $P < 0.05$), $ID_{50} = 0.52$ mg/kg (Fig. 2). Both quantal (not shown) and quantitative measurements yielded the same results. Response rates were not affected ($F(5,2) = 0.94$, $P > 0.05$).

Administration of WAY-100635 alone did not induce significant drug-lever responding ($\chi^2(2) = 0.1$, $P > 0.05$) (Table 1) but response rates were altered ($F(2,3) = 35.81$, $P < 0.05$). When tested together with flesinoxan (1.5 mg/kg) it dose dependently antagonized the flesinoxan cue ($\chi^2(4) = 16.9$, $P < 0.05$), with an $ID_{50} = 0.03$ mg/kg (Fig. 2). Both quantal (not shown) and quantitative measures yielded the same results. Response rates were unaffected ($F(4,1) = 39.02$, $P > 0.05$).

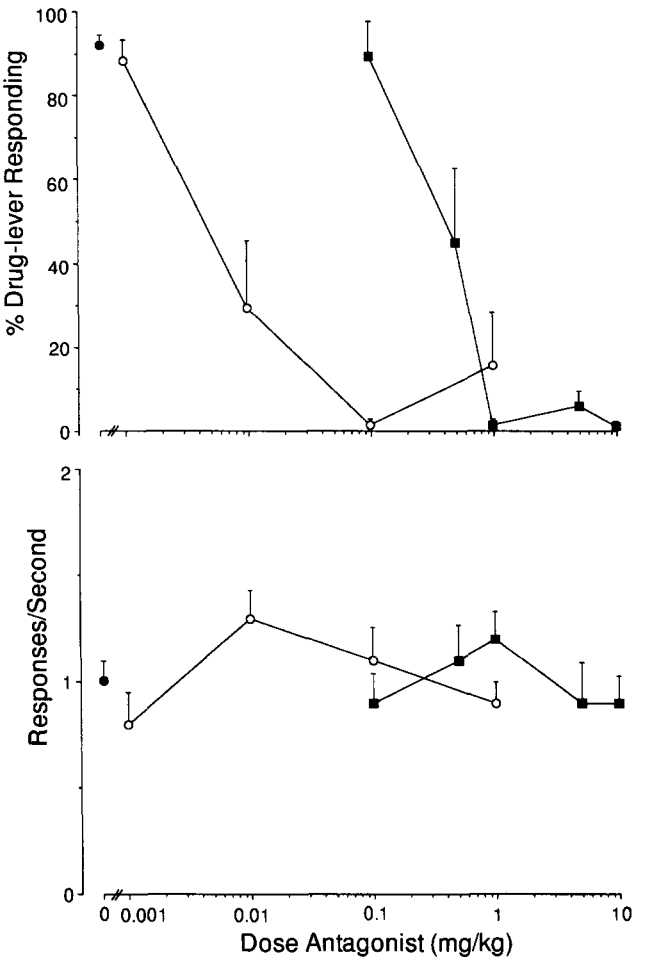

Fig. 2. Results of antagonism tests with the 5-HT_{1A} receptor antagonists WAY-100635 (○) and (*S*)-UH302 (■) and saline (●), coadministered with (+)-flesinoxan (1.5 mg/kg). Ordinate upper panel: mean percentage of responses on the (+)-flesinoxan appropriate lever (±S.E.M.). Ordinate lower panel: response rate (responses/second) (±S.E.M.). Abscissa: dose plotted on a log scale.

Fentanyl did not antagonize the flesinoxan stimulus significantly ($\chi^2(2) = 0.7$, $P > 0.05$) (Table 1). At the highest dose tested only three animals responded,

Table 1
Results of generalization and antagonism studies with (+)-flesinoxan (1.5 mg/kg p.o., −45 min) as the training drug

Drug	Dose (mg/kg)	*n* [a]	% Drug-lever responding [b]	% Drug-lever selection [c]	Resp/s (±S.E.M.) [d]
Water		8/8	3.2	0.0	1.5 (0.15)
Saline s.c.		8/8	15.2	12.5	1.5 (0.13)
(*S*)-UH301 s.c.	10.0	8/8	11.8	0.0	0.3 (0.07)
WAY-100635 s.c.	0.1	6/6	2.9	0.0	0.9 (0.08)
	1.0	7/7	29.9	28.6	0.8 (0.12)
Saline s.c. + flesinoxan		8/8	93.9	100.0	1.1 (0.15)
Fentanyl s.c.	0.03	6/6	56.6	66.7	0.7 (0.13)
+ flesinoxan	0.04	3/6	38.9	33.3	0.3 (0.17)

[a] Number of animals responding/number of animals tested. [b] Percentage of responses made on the drug-appropriate lever before obtaining the first reinforcement. [c] Percentage of animals selecting the drug-appropriate lever. [d] Mean number of responses/s.

which is inadequate for a statistical analysis. The quantal measurement showed that after 0.03 mg/kg fentanyl 4 out of 6, and after 0.04 mg/kg fentanyl 1 out of 3 animals selected the drug appropriate lever.

Without considering the highest dose there was a significant effect on response rates ($F(1,4) = 42.56$, $P < 0.05$).

4. Discussion

The present study shows that rats can learn to discriminate orally administered (+)-flesinoxan from water. The initial dose used (1.0 mg/kg) was apparently too low to yield stable drug-vehicle discrimination, but after raising the dose to 1.5 mg/kg the rats demonstrated stable performance throughout the study.

(+)-Flesinoxan generalized to both (−)-flesinoxan and the racemate, showing that both enantiomers have similar discriminative stimulus effects, indicating that they behave as 5-HT_{1A} receptor agonists. The ED_{50} values show that (−)-flesinoxan was a factor 8 less potent than its (+)-enantiomer. The ED_{50} values corresponded well with the affinities for the 5-HT_{1A} receptor: (+)-flesinoxan $K_i = 1.7$ nM, (−)-flesinoxan $K_i = 15$ nM, racemate $K_i = 4.7$ nM (Tulp, personal communication), showing that the difference in potency can be explained by the difference in affinity for the 5-HT_{1A} receptor. This strongly indicates that the stimulus properties of flesinoxan enantiomers are caused by activation of the 5-HT_{1A} receptor.

Flesinoxan did not generalize to (*S*)-UH301 or WAY-100635, indicating that (*S*)-UH301 and WAY-100635 have no 5-HT_{1A} receptor (partial) agonistic properties. In addition both compounds dose dependently antagonized the flesinoxan stimulus, further supporting the notion of (+)-flesinoxan exerting a 5-HT_{1A} receptor-mediated cue. Although (*S*)-UH301 and WAY-100635 have been suggested to be silent 5-HT_{1A} receptor antagonists, in this experiment both compounds reduced response rates when administered separately. The effect of (*S*)-UH301 appeared to be stronger than the effect of WAY100635. (*S*)-UH301 is known to have affinity for other receptors besides the 5-HT_{1A} receptor, e.g. dopamine receptors (Hillver et al., 1990). Therefore they could be involved in the stronger reduction of response rates produced by (*S*)-UH301.

Fentanyl administration before flesinoxan resulted in less than 80% drug-lever responding (suggesting partial antagonism), but statistical analysis showed no significant effect. One of the reasons for this is probably the low number of animals that responded. When lever selection was used as the dependent variable, 4 out of 6 (0.03 mg/kg) and 1 out of 3 (0.04 mg/kg) animals selected the drug lever. This suggests that fentanyl reduced the ability of flesinoxan to produce drug lever selection, but did so only at doses that reduced the overall rate of responding, and failed to block completely the discriminative stimulus of flesinoxan. Together with previously reported data on the ability of fentanyl and morphine to attenuate the discriminative stimulus effects of 8-OH-DPAT (Powell et al., 1994), the present data suggest that opioid receptor agonist–5-HT_{1A} receptor agonist interactions in drug discrimination may merit further examination.

Acknowledgements

We thank Dr. Martin Tulp for supplying us with receptor binding data.

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