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Risperidone (R 64 766), a potent and complete LSD antagonist in drug discrimination by rats

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Abstract. Risperidone was studied in a 0.16 mg/kg LSD-saline drug discrimination test procedure. At doses varying from 0.0025 to 0.63 mg/kg, no LSD-like agonist effects were observed. Studies on the antagonism of the LSD-cue indicated that risperidone was able to completely block the discriminative stimulus properties of LSD with a minimum ED_{50}-value of 0.028 mg/kg. Risperidone was also very active over time with reference to LSD antagonism, the ED_{50}s after 2, 4 and 8 h pretreatment being 0.028, 0.064 and 0.44 mg/kg. Response rate reductions were only observed at doses $\geqq$0.16 mg/kg after 1 h and at 0.63 mg/kg after 2 h pretreatment. Four and 8 h after treatment, no rate-reducing effects were apparent at doses up to 2.50 mg/kg. Thus at pretreatment intervals ranging between 2 and 8 h, complete antagonism of LSD without any rate effects was obtained. As compared to other LSD antagonists, risperidone was quantitatively better than setoperone and ritanserin and longer acting than pirenperone. Based on the pharmacological profile of risperidone and the other LSD antagonists, it was concluded that a potent central 5-HT_2 and catecholamine antagonism is needed for a potent and complete antagonism of the 0.16 mg/kg LSD-cue. The potential clinical effect of risperidone in the positive and negative symptoms of schizophrenia is discussed.

Key words: LSD-cue – Drug discrimination – Risperidone – Schizophrenia – 5-HT_2-catecholamine antagonism – LSD antagonism – Rat

Since the early work of Hirschhorn and Winter (1971) indicating that rats can discriminate LSD from saline, a considerable number of investigations have been carried out to characterize the LSD cue. Different conclusions were drawn from these studies. Firstly, it was demonstrated that stimulus generalization with LSD in the rat represents a necessary, albeit not sufficient condition, for the prediction of hallucinogenic activity in man (Winter 1975, 1978, 1980; Kuhn et al. 1977; Rosecrans and Glennon 1979; Appel et al. 1982). Secondly, the discriminative stimulus properties of LSD have been demonstrated to be contingent upon agonist effects at 5-HT (Kuhn et al. 1978; Winter 1978; Colpaert et al. 1982), and in particular 5-HT_2 receptors (Glennon et al. 1984; Cunningham and Appel 1987) in the brain, although there are also interactions at 5-HT_1 (Colpaert and Janssen 1983; Titeler et al. 1988) and other (e.g., dopamine, histamine or norepinephrine) receptors (Cunningham and Appel 1987). Thirdly, classical putative serotonin antagonists like cyproheptadine and methysergide act as partial and mixed agonist-antagonists in a 0.16 mg/kg LSD-saline drug discrimination procedure (Colpaert et al. 1979, 1982). Fourthly, pure LSD antagonists without any agonist activity (Colpaert et al. 1982, 1985; Colpaert and Janssen 1983) and with a high selectivity for 5-HT_2 as compared to 5-HT_1 receptors (Colpaert and Leysen 1981; Leysen et al. 1982, 1985; Leysen 1987) have been described. Lastly, and this in spite of any proposed pharmacological mechanism of action of LSD, it has been suggested that the discriminative effects LSD in rats are homologous to the subjective effects of this drug in humans (Colpaert 1984a; Colpaert et al. 1985).

The subjectively reported effects of LSD in humans are multiple, including feelings of tension, anxiety and depressed mood (Salvatore and Hyde 1956; Cohen 1967; Freedman 1968, 1969) as well as hallucinations, especially at higher doses (Abramson et al. 1955; Isbell 1959). Different evidences support the view that the subjective feelings of LSD in man may be closely related to the discriminative effects produced by 0.16 mg/kg LSD in animal models. Firstly, yohimbine a drug that also elicits subjective feelings of anxiety and tension in man (Holmberg and Gershon 1961; Charney et al. 1983), produces a cross generalization with LSD in a drug discrimination test procedure (Colpaert 1984b). Secondly, ritanserin and pirenperone, two pure LSD-antagonists, have been demonstrated to possess anxiolytic activities in animal models of anxiety (Colpaert et al. 1985; Meert 1986; Meert and Colpaert 1986). Furthermore, ritanserin is clinically described as an original thymostenic effective in anxiety and dysthymic disorders (Hoppenbrouwers et al. 1986; Reyntjens et al. 1986; Bressa et al. 1987). Thirdly, the LSD-antagonist setoperone has been clinically proven to exert an antipsychotic activity (Ceulemans et al. 1985).

The present study reports on the agonist and antagonist effects of 3-(2-(4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl)ethyl)-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido(1,2-a)-pyrimidin-4-one (R 64766; generic name: risperidone) in a 0.16 mg/kg LSD-saline discrimination procedure. Risperidone has been characterized as a centrally acting very potent serotonin 5-HT_2 and catecholamine (primarily dopamine-D_2) antagonist (Janssen et al. 1988).

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Materials and methods

Animals. Fifteen male Wistar rats weighing 240±20 g at the beginning of the experiment were used. The animals were housed individually in standard living cages. All housing and testing took place in a continuously illuminated and air-conditioned room (temperature: 21±1° C; relative humidity: 65±5%). Tap water was freely available. Access to dry powdered standard laboratory food was limited (see below).

Apparatus. Six test cages (Coulbourn instruments) fitted with a house light and two levers were programmed by solid-state logic modules. Between the two levers, a food pellet receptacle was mounted 2 cm above the floor of the cages. The cages were placed in a light- and sound-attenuating outer box.

Procedure. The drug discrimination procedure has been described in detail elsewhere (Colpaert et al. 1982). Daily discrimination training started after habituation and initial shaping to lever pressing for food on a fixed ratio 10 (FR = 10) schedule. Fifteen minutes before being placed in the test cage, the rat was injected IP with either 0.16 mg/kg *d*-LSD tartrate or physiological saline. Depending on whether the rat was injected with LSD or saline, it obtained food by pressing either the drug lever (DL) or the saline lever (SL) respectively. After every tenth press (FR 10) on the correct lever, a 45 mg food pellet was delivered by a food dispenser. Responses on the incorrect lever (i.e., the SL after LSD or the DL after saline) had no consequences. The lever assignments were DL-left, SL-right in about half of the animals and SL-left, DL-right in the other half. These assignments remained unchanged throughout the study. The number of responses made on either lever before the first reinforcement was obtained, and thus the point at which ten responses were made on the appropriate lever, was thus recorded (FRF-value). Fifteen minutes after the rat was placed in the test chamber, the session was terminated and all responses on both levers were recorded. The response rate (i.e., the sum of the responses on both the DL and SL) and the percentage responding on the selected lever (i.e., the ratio of the number of responses on the appropriate lever to the response rate) were calculated. After the session the animal was removed to its living cage. Two hours later, it was allowed to feed freely for 1 h. On weekends no sessions were run and the animals were given free access to food between 10 A.M. and 12 noon.

Every week, each rat was run once daily on 5 consecutive days. Daily training drug (D) or saline (S) injections were given according to two monthly alternating sequences, i.e., 1) D-S-S-D-S, S-D-D-S-S, S-D-S-D-D, D-S-D-S-D and 2) S-D-D-S-S, D-S-D-S-D, D-S-S-D-D, S-D-S-D-S. Rats whose sequential numbers were odd were run according to one sequence, whereas even-numbered animals were run according to the alternative sequence. Discrimination training proceeded individually for each rat until ten consecutive sessions occurred in which a FRF-value $\leq$13 was obtained. Animals reaching this criterion were used for testing.

Test sessions were run on Fridays only and the training procedure was continued on the remaining days. On test days, the animal was given the treatment being studied and was put in the operant chamber at a specified time after the treatment. It was then noted on which of the two levers the animal first made a total of ten responses. This lever is referred to as the selected lever. Once this lever selection was established, the rat obtained a first food pellet and subsequent reinforcement was contingent upon pressing (FR10) the selected lever. Testing was postponed to the next test day if the FRF-value exceeded 14 on either of the 3 most recent training days. In addition, test data were discarded and the test condition later retested if the FRF-value during testing exceeded 14.

Before being used in tests, the animals were given 1 week of habituation to a double treatment condition. That is, before every saline or LSD injection at 15 min prior to testing (i.e., t−15), the animals were always given an additional subcutaneous injection of saline 60 min prior to the test. The double treatment on training days was continued for the duration of the experiments.

The doses of risperidone that were studied are specified below (see Drugs). Risperidone was examined in two sets of experiments that were designed to determine its possible LSD-antagonist and LSD-like agonist effects. To test for LSD antagonism, risperidone or the solvent was injected subcutaneously (SC) at either 60, 120, 240 or 480 min before testing and was followed by 0.16 mg/kg LSD (IP, at t−15 min). To test for agonist effects, risperidone or the solvent was injected SC at t−60 min and saline IP at t−15 min before testing. The doses of risperidone that were tested were selected on the basis of preliminary experiments in a separate pool of trained rats. Each range extended from doses that were inactive up to doses that were active in all rats. Each test condition was tested in five rats. The rats were randomly selected to participate in the tests on antagonist or agonist drug effects. Once a rat was selected for a particular experiment, all doses and the vehicle solution were tested within this rat.

Drugs. The drugs used were risperidone (Janssen et al. 1988) and *d*-lysergic acid diethylamine tartrate (LSD). Aqueous solutions were used of LSD and of risperidone using 2 equivalents tartaric acid. The doses were selected from the geometrical series 0.00063, 0.0025, ..., 0.63, 2.50 mg/kg and were thus successively increased by a factor of four. If a change in lever selection occurred, an additional intermediate dose (i.e., a two- instead of a four-fold increment) was tested between the two doses with reference to which the change in lever selection was seen. All doses of drugs, saline or vehicle were administered in a volume of 1 ml/100 g body weight.

Statistics. The Wilcoxon matched-pairs signed-ranks test (Siegel 1956; two-tailed) was used throughout in order to evaluate differences between drug and vehicle treatments. ED_{50}-values and 95% confidence limits were calculated according to Finney's iterative method (Finney 1971).

Results

An example of the individual data obtained in the drug discrimination studies and the calculation of derived parameters are given in Table 1. In this table, the results of five rats treated with 0.04 mg/kg risperidone (SC; t−60) and 0.16 mg/kg LSD (upper panel) or saline (lower panel) are given.

Globally, at none of the doses (0.0025–0.63 mg/kg) tested did risperidone produce any stimulus generalization

Table 1. Individual results of five rats treated with 0.04 mg/kg risperidone plus 0.16 mg/kg LSD (*upper panel*) or plus saline (*lower panel*)

	Rat #	Selected lever	FRF value	Drug lever responses	Saline lever responses	Total response rate	% responding selected lever	Total response rate last saline session	Response rate as % of last saline session
With LSD	1	SL	10	2	710	712	99.72	631	112.84
	2	DL	10	1418	0	1418	100.00	1150	123.30
	3	SL	12	80	1769	1849	95.67	2011	91.94
	4	DL	11	1660	2	1662	99.88	1642	101.22
	5	SL	11	1	940	941	99.89	1023	91.98
$\bar{x}$			10.80				99.03		104.26
S.E.M.			0.37				0.84		6.12
Without LSD	1	SL	11	1	520	521	99.81	820	63.54
	2	SL	12	2	1750	1752	99.89	1727	101.45
	3	SL	11	1	1290	2291	99.92	1311	98.47
	4	SL	10	0	630	630	100.00	761	82.79
	5	SL	10	0	1910	1910	100.00	1881	101.54
$\bar{x}$			10.80				99.92		89.56
S.E.M.			0.37				0.04		7.37

Risperidone was injected SC at 60 min prior to testing and LSD or saline IP at 15 min before test. The lever selection, the FRF-value, the number of responses on the drug and the saline lever, and the total response rate are given within a session. The % responding on the selected lever is the ratio of the response rate on the selected lever to the total response rate. Response rate as a % of last saline session represents the ratio between the total response rate in the test session and the rate during the last saline session. Based on the lever selection, the percentage of rats selecting the drug lever was calculated for each treatment condition as was the mean (±1 SEM) of the FRF-values, the % responding on the selected lever and of the response rate as a % of the rate during the last saline session

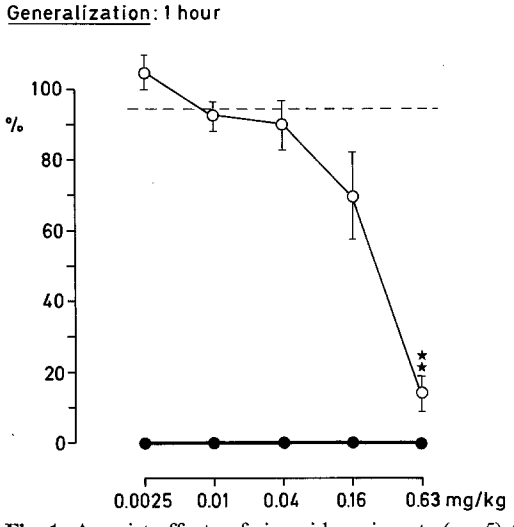

Fig. 1. Agonist effects of risperidone in rats ($n=5$) trained to discriminate 0.16 mg/kg LSD from saline. Risperidone was injected SC 60 min before test and 45 min before the IP injection of saline. *Abscissa:* dose of risperidone in mg/kg. The *ordinate* expresses the percentage of rats selecting the DL (*bold line*) and the response rate (*thin line*). Animals not selecting the DL selected the SL. Response rate (mean ± SEM) expressed the number of responses made on a test session as a percentage of responses on the most recently preceding saline session. Two *asterisks* indicate $P<0.01$ (two-tailed, Wilcoxon test; Siegel, 1956) for the difference between the test result and the vehicle result (*horizontal dotted line*)

with LSD (Fig. 1). The failure to produce any stimulus generalization with LSD was also reflected in the FRF-values and the percentage responding on the selected lever (i.e., here the saline lever, SL) (Fig. 3, left panel). At no time was an average FRF-value >11.00 or a percentage responding on the saline lever ≦99.00% observed, except for 0.63 mg/kg risperidone. At this dose, a mean (±SEM) rate of 79.16 (±8.15)% on the SL was obtained although the average FRF-value was 10.20 (±0.20). Rats treated with 0.63 mg/kg risperidone thus started to make some responses on the DL after first having selected the SL correctly. No differences ($P>0.05$) were observed between risperidone- and vehicle-treated rats in terms of FRF-values and in terms of percentage responding on the SL. In terms of response rate (expressed as a percentage of the rate during the last saline session), a significant ($P<0.01$) reduction occurred between vehicle- and 0.63 mg/kg risperidone-treated rats (Fig. 1). At 0.63 mg/kg, the average response rate decreased from a vehicle- control level of 93.99 (±2.33) to 13.63 (±4.36)%.

Risperidone antagonized completely the effects of 0.16 mg/kg LSD in a dose-dependent manner over time. The ED_{50}s (95% confidence limits) for LSD antagonism at 1, 2, 4 and 8 h after treatment were 0.028 (0.015–0.051), 0.028 (0.014–0.056), 0.064 (0.034–0.12) and 0.44 (0.23–0.85) mg/kg, respectively (Fig. 2). At no time were there any average FRF-values >11.00. Per cent responding on the selected lever always exceeded 99.00% except for 0.16 mg/kg at 1 h and 0.16 and 0.63 mg/kg at 2 h after treatment. Under these conditions, mean rates of 89.01 (±4.63), 97.45 (±2.52) and 97.92 (±0.76)% were measured (Fig. 3). No differences ($P>0.05$) between the vehicle- and risperidone-treated rats were found for the average FRF-values and mean per cent responding on the selected lever. As compared to the vehicle, risperidone reduced ($P<0.05$) the response rate starting from 0.16 mg/kg at 1 h and at 0.63 mg/kg at 2 h after treatment. After 4 and 8 h, no rate reducing effects were apparent any longer at doses up to 0.63 and 2.50 mg/kg, respectively.

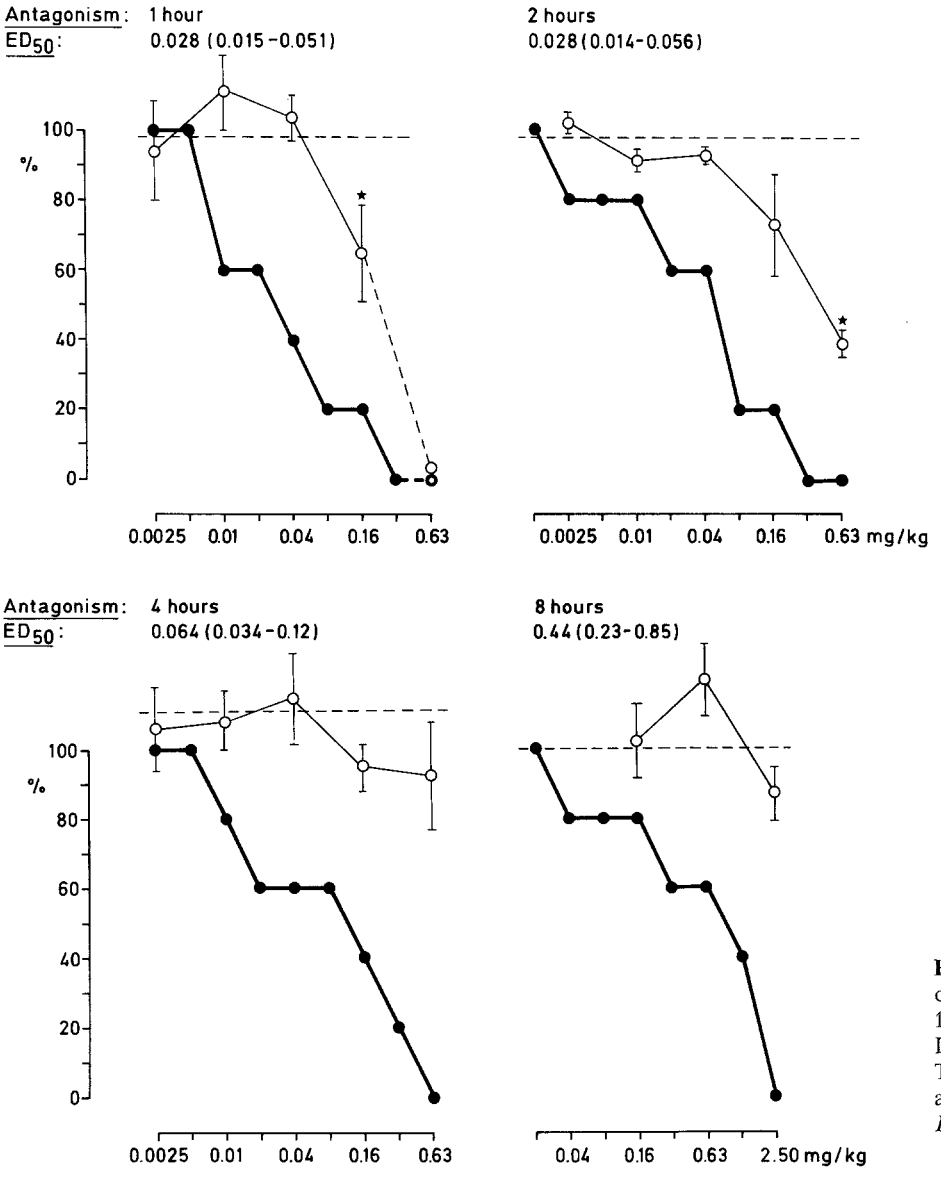

Fig. 2. Antagonist effects of risperidone over time. Risperidone was injected SC at 1, 2, 4 and 8 h before test and 0.16 mg/kg LSD was injected IP at 15 min before test. The ED_{50}s (and 95% confidence limits) are given in mg/kg. One asterisk indicates $P<0.05$. See also legend to Fig. 1

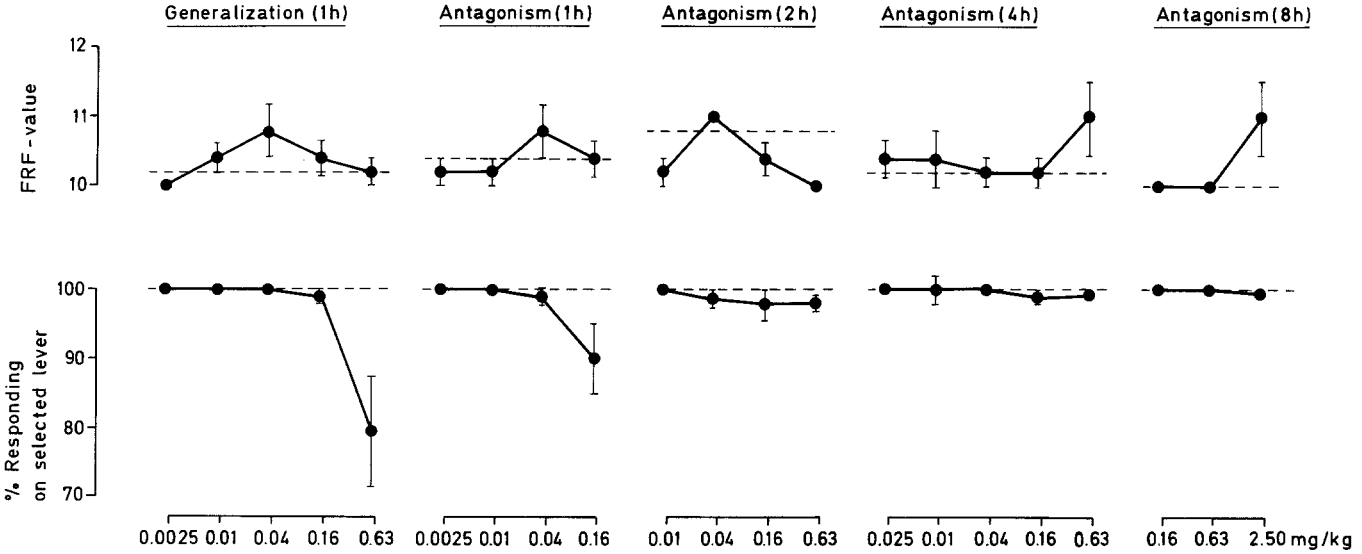

Fig. 3. FRF-values and percentage responding on the selected lever, of rats treated with risperidone plus saline (generalization) and risperidone plus LSD (antagonism). Each point represents the mean (±1 SEM) of five rats. *The dotted lines* represent the corresponding vehicle control levels. No differences (Wilcoxon test, two-tailed, $P>0.05$) between the test and the vehicle results were observed

Discussion

The LSD agonist and antagonist properties of the very potent central acting serotonin 5-HT_2 and catecholamine antagonist risperidone (Janssen et al. 1988) were studied in a 0.16 mg/kg LSD-saline drug discrimination test procedure. At doses ranging from 0.0025 up to 0.63 mg/kg, no LSD-like agonist effects were observed (Fig. 1). Studies on the antagonism of the 0.16 mg/kg LSD cue indicated that risperidone was able to completely block the discriminative stimulus properties of 0.16 mg/kg LSD (Fig. 2). The antagonism of LSD started at very low doses (0.0025–0.01 mg/kg), was dose related and reached a 100% level of effect at doses varying from 0.31 to 2.50 mg/kg, according to the pretreatment time. The antagonism of the LSD cue was time dependent, with the ED_{50}s at 1, 2, 4 and 8 h of 0.028, 0.028, 0.064 and 0.44 mg/kg, respectively. Thus globally, no generalization was observed with doses 22.5 times higher than the lowest ED_{50} for LSD antagonism.

Rate-diminishing effects were observed at 1 and 2 h after treatment at doses starting from 0.16 mg/kg risperidone. Because at these intervals a complete LSD antagonism in all five tested rats required a dose of 0.31 mg/kg, there is some overlap here between the doses that affect response rate and those needed for complete LSD antagonism in all rats. However, based on the average response rate and the first dose that affected the response rate, it could be concluded that the rate-reducing effects at two hours were much less pronounced than at 1 h after treatment. Furthermore, at 4 and 8 h after treatment no effects on response rate were present up to 2.50 mg/kg. Thus after intervals as long as 2 h, a complete antagonism of LSD can be obtained without any side effects. These results indicate that the mechanism responsible for the rate-depressing effects very quickly diminishes over time and that this mechanism is independent of the mechanism responsible for complete LSD antagonism.

Because risperidone produced a complete LSD antagonism without any LSD-like agonist properties, the compound clearly differs from classical putative 5-HT antagonists like cyproheptadine, metergoline and methysergide (Colpaert et al. 1979, 1982). Risperidone more closely resembles pirenperone (Colpaert et al. 1982; Colpaert and Janssen 1983), setoperone (Colpaert et al. 1984) and ritanserin (Colpaert et al. 1985), three other pure LSD antagonists. The reported ED_{50}s of pirenperone, setoperone and ritanserin 1 h after subcutaneous treatment are 0.02, 0.32 and 11.6 mg/kg, respectively. With a lowest ED_{50} of 0.028 mg/kg, risperidone thus appears to be as potent as pirenperone in antagonizing the LSD cue. Risperidone is, however, longer acting than pirenperone. Therefore, risperidone is a more potent LSD antagonist than pirenperone, setoperone and ritanserin.

The data on LSD antagonism discussed here indicate that pirenperone and risperidone, two potent centrally acting 5-HT_2 antagonists with pronounced catecholamine antagonistic properties (Meltzer et al. 1983; Colpaert and Janssen 1984; Janssen et al. 1988), are very potent LSD antagonists. Ritanserin, a selective central acting 5-HT_2 antagonist (Awouters et al. 1988; Meert et al. 1987b), is a much weaker LSD antagonist. These results demonstrate that additional to a central 5-HT_2 receptor blockade, a central catecholamine antagonism facilitates the antagonism of the LSD cue. The LSD cue is thus primarily 5-HT_2-but also catecholamine-mediated (Cunningham and Appel 1987). It is of interest that a similar relationship was observed for the antagonism of 5-HTP-induced head twitches. Although 5-HTP-induced head twitches are primarily 5-HT_2 receptor-mediated, a catecholamine component is also present (Meert et al. 1988).

Because the discriminative stimulus properties of LSD in the rat are homologous to the subjective effects of this drug in man (see introduction), it is possible that antagonists of the LSD cue possess anxiety-, tension- and depression-reducing properties as well as an antihallucinogenic activity. For the LSD antagonists ritanserin and pirenperone, anxiolytic effects have been described both experimentally (Colpaert et al. 1985; Meert 1986; Meert and Colpaert 1986) and clinically (Ansseau et al. 1983; Hoppenbrouwers et al. 1986; Bressa et al. 1987). Furthermore, in humans, ritanserin had clear mood-elevating properties, and in combination with classical neuroleptics, the drug had an effect on both the positive and negative symptoms of schizophrenia (Hoppenbrouwers et al. 1986; Reyntjens et al. 1986). The LSD antagonist setoperone was demonstrated to have clinical antipsychotic activity (Ceulemans et al. 1985). Setoperone was found to be effective in schizophrenia and to induce fewer EPS than classical neuroleptics (Ceulemans et al. 1985).

Risperidone resembles setoperone in that they are both central-acting 5-HT_2 and D_2 receptor antagonists, with risperidone being more potent. Risperidone was observed to improve both the positive and negative symptoms of schizophrenia without inducing EPS (Janssen 1987; Meert et al. 1987a). In terms of clinical efficacy, risperidone resembles combined treatment of ritanserin and haloperidol. The idea that LSD antagonists may possess antipsychotic activity is also supported by studies using the acoustic startle paradigm. In different studies applying this technique, it was observed that LSD-treated rats revealed habituation deficits to the acoustic stimuli similar to those exhibited by schizophrenic patients. Furthermore, both 5-HT_2 and catecholamine mechanisms are thought to be involved in these modulations of the acoustic startle (Geyer et al. 1978; Geyer and Braff 1982, 1987).

In conclusion, risperidone was found to be a potent, complete and relatively long acting antagonist of the discriminative stimulus properties of 0.16 mg/kg LSD in the rat. In this regard, risperidone thus resembles pirenperone, setoperone and ritanserin, although it is a more potent and longer-acting LSD antagonist. Risperidone, with its very potent central 5-HT_2 and catecholamine (especially dopamine D_2) receptor antagonistic properties, thus seems to be a very selective LSD antagonist. Clinically, risperidone can be used for antipsychotic therapy, producing contact and mood improvement without much induction of EPS.

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