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The $5HT_2$ Antagonist Pirenperone Reverses Disruption of FR-40 by Hallucinogenic Drugs[1]

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MOKLER, D. J., K. W. STOUDT AND R. H. RECH. *The $5HT_2$ antagonist pirenperone reverses disruption of FR-40 by hallucinogenic drugs.* PHARMACOL BIOCHEM BEHAV 22(5) 677–682, 1985.—Indolealkylamine and phenethylamine hallucinogens disrupted responding maintained under a fixed-ratio 40 (FR-40) schedule of reinforcement. LSD, DMT, mescaline and DOM produced dose-dependent decreases in number of reinforcers and increases in 10-sec periods of non-responding (pause-intervals). The 5HT agonist quipazine, as well as the LSD congener lisuride, altered response patterns in a similar manner. The effects of these drugs were examined after pretreatment with pirenperone, an antagonist with specificity toward the $5HT_2$ receptor with reference to the $5HT_1$ receptor. The dose-response curves for the phenethylamine hallucinogens were shifted significantly to the right and to a greater degree than were those for the indolealkylamine hallucinogens. Pirenperone also antagonized the effects of quipazine to a degree similar to that observed with the phenethylamine-type hallucinogens. Pirenperone did not significantly shift the dose-response pattern to lisuride. These data suggest that the behavioral disruption induced by these hallucinogens and quipazine relates at least in part to an effect on $5HT_2$ receptors, while the effects of lisuride do not involve a significant interaction at the $5HT_2$ receptor.

Hallucinogens Pirenperone FR-40 operant behavior Quipazine Lisuride 5HT receptors

HALLUCINOGENIC drugs appear to influence various behaviors in experimental studies with animals by altering activity of brain 5-hydroxytryptamine (5HT) neuronal systems [14,29]. Disruption of fixed-ratio 40 (FR-40) operant behavior by indolealkylamine and phenethylamine hallucinogens was potentiated by agents that depleted brain 5HT and attenuated by 5HT antagonists [6, 20, 28], but not by treatments that interfered with brain catecholamine mechanisms [4,18]. Therefore, this effect of the hallucinogens on response patterns in the FR-40 schedule does not appear to involve influences on brain dopaminergic or noradrenergic systems. In addition, the discriminability of hallucinogens by animals performing in operant behavioral procedures is also blocked by 5HT antagonists [1, 3, 11]. Therefore, while the effects of hallucinogenic agents may be conditioned to some extent by actions on catecholamine receptors, their actions on 5HT mechanisms appear to be more directly related to the behavioral effects of these drugs in animals.

Recent evidence suggests the existence of multiple 5HT receptors in brain [2, 18, 26, 27]. The receptor that manifests a high affinity for 5HT has been termed the $5HT_1$ receptor, whereas the receptor with a low affinity for 5HT but which is labeled by ^{3}H-spiroperidol has been called the $5HT_2$ receptor. The $5HT_1$ receptor may mediate the inhibitory effects of 5HT, while the $5HT_2$ receptor may be involved in certain excitatory effects of 5HT [27]. An autoreceptor on raphe cell bodies, activation of which inhibits cell firing [19], may be presumed to be a third variety of receptor, since it differs pharmacologically from the other two.

Pirenperone and ketanserine are thought to be somewhat specific antagonists at the $5HT_2$ receptor [15–17]. Colpaert *et al.* [3] have reported that pirenperone antagonizes the cues produced by lysergic acid diethylamide (LSD) in rats trained to discriminate LSD from saline. Furthermore, in rats trained to discriminate the phenethylamine hallucinogen 2,5-dimethoxy-4-methylamphetamine (DOM) from saline, the discrimination is blocked by both pirenperone and ketanserine [11].

The present work describes the antagonistic effects of pirenperone on the disruption of operant behavior induced by the indolealkylamine hallucinogens LSD and N,N-dimethyltryptamine (DMT) and the phenethylamine hallucinogens mescaline and DOM. The disruption induced by the 5HT agonist quipazine or the LSD congener lisuride and antagonistic effects of pirenperone against these non-hallucinogenic agents are also examined.

[1]The results of this study were included in a thesis submitted by DJM to Michigan State University in partial fulfillment of requirements for the Ph.D. degree. A preliminary communication was presented at the 1983 Annual Meeting of the Society for Neuroscience in Boston, MA.

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METHOD

Subjects

Male Sprague-Dawley rats (Harlan Sprague-Dawley, Indianapolis, IN) were acclimated to the laboratory for two weeks before initiating behavioral training. The subjects were housed individually in a room with a 12-hour light-dark cycle and controlled temperature and humidity. They were food-deprived to 80% ad lib body weight and allowed free access to water.

Procedure

Animals were placed in operant chambers (LVE 143-20-215) at the same time of day, six days a week, for 40-min sessions. The subjects were trained to press a bar (10–15 g force required) under a fixed-ratio 40 (FR-40) schedule for 45 mg food pellets (BioServ, Inc., Frenchtown, NJ). The number of reinforcers received and the number of 10-sec periods of non-responding (pause intervals, [6,24]) were recorded on electromechanical counters. A pause interval was registered when a subject failed to make a response on the operant lever for a period of 10 sec. Programming was controlled by electromechanical circuits.

Drugs

Drugs and vehicles were administered IP in a random pattern before the session on every Wednesday or Saturday with the sessions on Monday, Tuesday, Thursday and Friday serving as control days. The data obtained following drug administration were compared with the data obtained on the control day immediately before. LSD tartrate, DMT fumarate, mescaline HCl, 2,5-dimethoxy-4-methylamphetamine (DOM) HCl (National Institute on Drug Abuse, Rockville, MD), quipazine maleate (Miles Labs., Elkhart, IN) and lisuride hydrogen maleate (a gift from Schering AG, Berlin, FRG) were dissolved in distilled water and were administered immediately before the session. Pirenperone (a gift from Janssen Pharmaceutics, Beerse, Belgium) was suspended in a solution of 0.5% methylcellulose in distilled water and administered 40 min prior to the beginning of the operant session. Concentrations of drug solutions were varied to allow for a standard injection volume of 1.0 ml/kg.

Statistics

Individual dose-response relationships were analyzed using a one-way analysis of variance (ANOVA) with the least significant differences test for comparisons. Comparisons between dose-response curves were accomplished using a two-way ANOVA with the least significant difference test for individual comparisons. ED50 values were determined using probit analysis; when warranted, values were transformed to the arcsin square-root.

RESULTS

The animals in this study received 153±11 reinforcers and produced 34±3 pause intervals (mean±S.E.M., n=22) during 40-min control sessions. Pirenperone (20–160 μg/kg) administered alone did not significantly alter responding from a saline control ($F(4,87)=0.63$ for pause intervals, one-way ANOVA).

LSD (25–800 μg/kg, 0 min pretreatment) produced a dose-dependent decrease in reinforcers accompanied by an increase in pause intervals (Fig. 1). The ED50 for the change

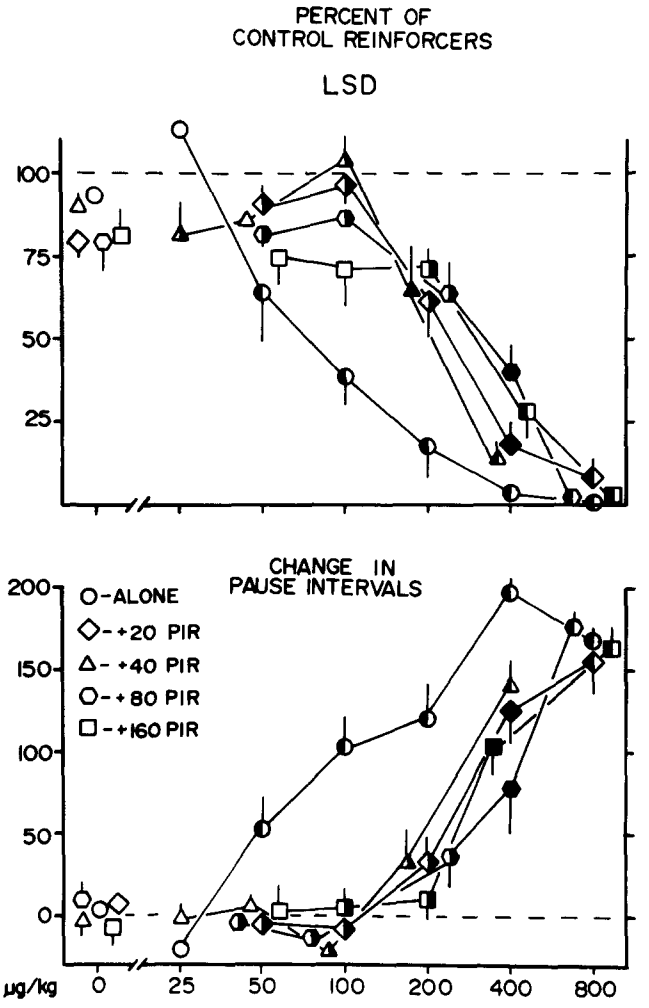

FIG. 1. The effects of LSD alone and in combination with various doses of pirenperone (n=8). Shading of the left half of the symbol represents a significant difference from control ($p<0.05$, one-way ANOVA, lsd test). Shading of the right half represents a significant difference from LSD alone ($p<0.05$, two-way ANOVA, lsd test). Doses of pirenperone are expressed in μg/kg.

in pause intervals induced by LSD was 103 μg/kg (Table 1). When pirenperone was administered prior to the administration of LSD, the dose-response curve for LSD was shifted significantly to the right for all doses of pirenperone studied. The attenuation of the effect of LSD on pause intervals was reflected in an increase in ED50 ratios from a low of 2.58 to a high of 3.63 after pretreating with 40 and 80 μg/kg pirenperone, respectively (Table 1). Combination of LSD with 20 or 160 μg/kg pirenperone yielded intermediate values.

Another indolealkylamine hallucinogen, DMT, disrupted operant behavior with an ED50 for pause intervals of 4.35 mg/kg (Table 1). DMT also produced a concomitant decrease in reinforcers (data not shown). Pirenperone pretreatment produced a dose-dependent antagonism of the effects of DMT on pause intervals. Pretreatment with pirenperone at a dose of 20 μg/kg increased the ED50 of DMT for pause intervals 1.6 times while 80 μg/kg shifted the ED50 3.45 times.

DOM disrupted FR-40 behavior at doses between 0.25 and 8.0 mg/kg, the ED50 for pause intervals being 0.84 mg/kg

TABLE 1

ED50S FOR CHANGE IN PAUSE INTERVALS FOR AGONISTS ALONE AND COMBINATIONS WITH PIRENPRONE

	Alone	+20 μg/kg PIR	+40 μg/kg	+80 μg/kg	+160 μg/kg
LSD (μg/kg)	103 (61–184)†	307 (2.98)* (213–443)	266 (2.58) (216–354)	374 (3.63) (290–552)	368 (3.57) (299–452)
DMT (mg/kg)	4.35 (3.6–5.43)	6.95 (1.60) (5.18–10.7)	7.69 (1.77) (5.98–10.7)	15.0 (3.45) (9.9–78.5)	— —
DOM (mg/kg)	0.84 (0.63–1.15)	3.93 (4.68) (2.84–6.79)	3.11 (3.70) (2.40–4.23)	4.59 (5.46) (3.63–5.87)	4.94 (5.88) (3.68–9.22)
Mescaline (mg/kg)	10.4 (7.8–17)	48.9 (4.70) (34–28201)	82.5 (7.93) (41–9458)	157 (15.10) (69–2614)	— —
Quipazine (mg/kg)	1.68 (1.38–5.88)	3.93 (2.34) (2.84–6.79)	3.88 (2.31) (3.04–5.11)	8.07 (4.80) (6.03–12.21)	13.4 (7.98) (4.8–923040)
Lisuride (μg/kg)	27 (20–40)	56 (2.07) (34–85)	37 (1.37) (31–46)	46 (1.70) (39–55)	37 (1.37) (27–53)

ED50s were determined by probit analysis.

*Dose ratio $= \frac{\text{ED50:agonist plus pirenperone}}{\text{ED50:agonist alone}}$

†95% confidence interval.

(Table 1). All dose levels of pirenperone very effectively antagonized the effects of DOM.

Mescaline affected behavior in a manner similar to the other hallucinogens, with a dose-dependent decrease in reinforcers and a concurrent increase in pause intervals (Fig. 2). Mescaline disrupted the operant behavior with an ED50 for pause intervals of 10.4 mg/kg (Table 1). The antagonism of mescaline by pirenperone was the most dramatic, compared with the other agonist-antagonist combinations examined; pretreatment with 80 μg/kg pirenperone shifted the ED50 to 157 mg/kg. Overall, this antagonism was dose-dependent.

The 5HT agonist quipazine produced a pattern of disruption similar to that of the hallucinogens. The ED50 for the effect of quipazine on pause intervals was 1.68 mg/kg (Table 1). Pirenperone shifted the dose-response curve of quipazine to the right, generally in a dose-dependent manner. ED50 ratios of quipazine ranged from 2.31 after 40 μg/kg pirenperone to 7.98 after 160 μg/kg pirenperone.

Lisuride was the most potent of the agonists studied, the ED50 for pause intervals being 27 μg/kg (Table 1). Once again, there was a reciprocal decrease in reinforcers with each dose-related increase in pause intervals. Pirenperone generally did not antagonize the effects of lisuride, no significant shift in dose-response curves being observed after any dose of the antagonist. However, a few single doses showed significant differences.

DISCUSSION

Pirenperone administered as a 40-min pretreatment did not significantly alter FR-40 behavior. This lack of effect differs from effects of other 5HT antagonists [6, 24, 29]. While cinanserin decreased both reinforcers and pause intervals significantly, metergoline and pizotifen increased reinforcers and decreased pause intervals [17]. Furthermore, cinanserin potentiated rather than antagonized the effects of

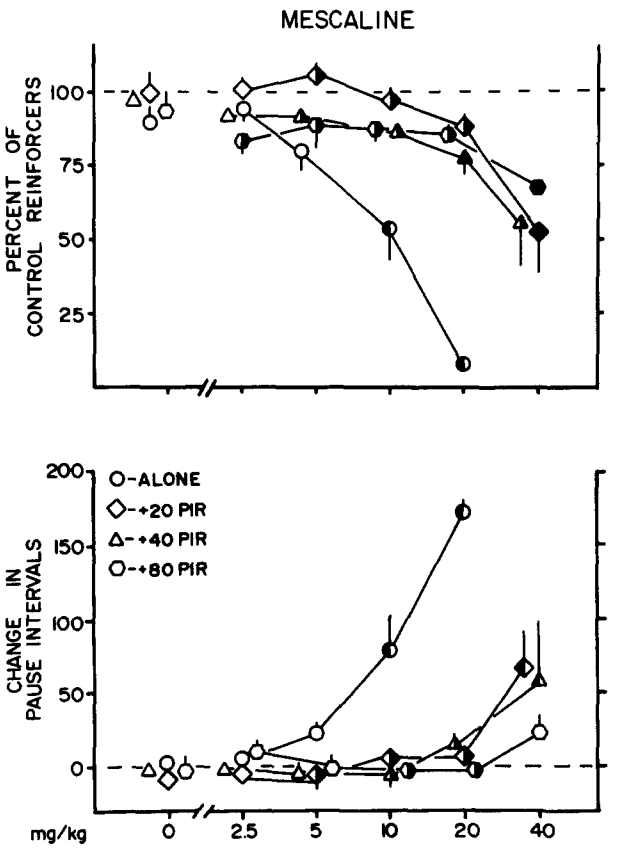

FIG. 2. Effects of mescaline alone and in combination with various doses of pirenperone (n=8). Shading of the left half of a symbol denotes a significant difference from control; shading of the right half denotes a significant difference from mescaline alone.

lisuride. Since pirenperone has been proposed to be a selective $5HT_2$ antagonist [15–17], while other 5HT antagonists interact with both $5HT_1$ and $5HT_2$ receptors [2, 16, 26, 27], the differences in behavioral effects among these antagonists are likely to reflect their differing propensities to interact with various types of 5HT receptors. In the present experiments, pirenperone may have interacted only at $5HT_2$ receptors, whereas metergoline and pizotifen may have blocked both $5HT_1$ and $5HT_2$ receptors, and cinanserin may have acted as a partial agonist at $5HT_1$ and an antagonist at $5HT_2$ receptors (for background see [3]). Pirenperone may also interact with dopaminergic receptors [15], although it seems unlikely that such effects relate to the interactions described here. Previous work from our laboratory implicated 5HT but not catecholaminergic mechanisms in the disruption of FR-40 behavior by these hallucinogenic agents [4, 6, 23, 24, 28]. Moreover, pirenperone exerts no significant dopamine agonist- or antagonist-type activity by itself, but antagonizes discriminative stimulus cues for the hallucinogens while dopamine antagonists do not [1,11].

The efficacy of pirenperone to antagonize the effects of hallucinogens was similar to the antagonism of the effects of hallucinogens by the other 5HT antagonists [6, 24, 29]. The dose range for pirenperone, chosen on the basis of previous studies [3, 15, 16], proved to be very effective even at the lowest dose in this range (20 μg/kg) to antagonize the disruption of operant behavior by LSD, DOM, and especially mescaline. Pirenperone also showed a greater efficacy to antagonize phenethylamine than indolealkylamine hallucinogens, though the difference was not as dramatic as previously observed with metergoline [6,28]. Perhaps phenethylamine hallucinogens exert more of their effects by way of $5HT_2$ than $5HT_1$ receptors, while LSD and DMT may have a relatively greater influence through $5HT_1$ receptors. Nevertheless, the broad antagonistic effects of pirenperone suggest that agonistic actions at $5HT_2$ receptors are at least a necessary component for the behavioral effects of these hallucinogenic drugs.

Quipazine also disrupted FR-40 operant behavior in the pattern characteristic of the hallucinogens, and this effect was antagonized by metergoline, pirenperone, and other 5HT antagonists [7,24]. It may be surmised that quipazine would be hallucinogenic in man. However, quipazine exerts at best very weak hallucinogenic phenomena in its clinical spectrum of activity [25,35]. Although quipazine effects on FR-40 performance resemble the pattern observed with hallucinogens and also appear to involve 5HT mechanisms, quipazine's actions must occur by a mechanism that is somewhat different. Indole and phenethylamine hallucinogens are potentiated in disrupting FR-40 behavior by pretreating the subjects with naloxone [5,22], while quipazine's disruption of FR-40 responding is antagonized by naloxone. Moreover, reduction of food intake by quipazine in a free-feeding situation occurs at the same doses as for the FR-40 decrements [12]. Reduction of intake by LSD and DOM during the free-feeding condition occurs at doses considerably greater than those disrupting the FR-40 performance (Henck and Rech, unpublished observations). Thus, quipazine's effects on FR-40 behavior probably involve a reduced motivation for food (for review, see [31]), whereas the hallucinogens probably disrupt the FR-40 operant pattern by way of an associational disturbance.

Comparison of quipazine and LSD in drug discrimination studies has also shown some subtle distinctions, but suggests that the actions of lower doses of indole and phenethylamine hallucinogens and quipazine are mediated at least in part by way of $5HT_2$ receptors [11, 35, 36]. Furthermore, the discriminative stimulus properties of lower doses of quipazine were correlated with *in vitro* binding to brain $5HT_2$ sites rather than $5HT_1$ sites by Friedman *et al.* [9]. Therefore, activation of $5HT_2$ receptors may be necessary but not sufficient to account for the hallucinogenic potential of agents that act through 5HT receptors.

The LSD congener lisuride is even more effective than LSD in suppressing the discharge of dorsal raphe neurons on iontophoretic administration, but, in contrast to LSD, iontophoretically-administered lisuride is a potent agonist at certain forebrain $5HT_1$ receptors [31]. On the other hand, lisuride was inactive when tested for the LSD effect on facial nucleus motoneurons to facilitate their discharge [19]. Moreover, this latter effect of LSD was antagonized by pretreating the subject with metergoline, cinanserin and other 5HT antagonists [20]. Excitatory effects of LSD have been presumed to be mediated by way of $5HT_2$ receptors [13, 21, 27], but by increased discharge of active neurons rather than by provoking silent cells to become active. Minimal involvement of $5HT_2$ mechanisms in the disruption of FR-40 behavior by lisuride is also suggested by the poor antagonism exerted by pirenperone in the present study. Although lisuride appears to exert dopaminergic activity in some contexts [1, 32–34], this aspect appears to have little consequence in disruption of the FR-40 paradigm [23]. Lisuride does not induce hallucinatory components in its clinical spectrum [1, 19, 34]. Perhaps this drug exhibits a predominance of $5HT_1$ agonistic actions, which may once more be necessary but not sufficient to induce hallucinations. This would explain the potentiation rather than antagonism of lisuride's disruptive effects by cinanserin [24], assuming that cinanserin is a partial agonist at $5HT_1$ receptors [3].

Appel and coworkers [1, 33, 34] have demonstrated differences between the effects of LSD and lisuride, suggesting that they act in part as agonists at different receptors. Lisuride generalized to the LSD cue in subjects trained to discriminate LSD from saline [33]. However, rats could also be trained to discriminate between LSD and lisuride. Moreover, the LSD cue was attenuated by classical 5-HT antagonists, while the lisuride cue was nullified by dopamine antagonists [1, 32, 34]. Nevertheless, there is ample evidence to indicate that lisuride does affect brain 5HT systems [1, 7, 19, 30, 34], and the disruption of FR-40 operant behavior by lisuride is antagonized by 5HT antagonists rather than by dopaminergic antagonists [23,24]. This is consistent with our other reports that the reciprocal pattern of decreased reinforcers and increased "pausing" induced by the hallucinogens is related to effects on 5HT receptors rather than on dopaminergic mechanisms [4, 6–8, 22, 28]. Therefore, although LSD and lisuride have some receptor interactions in common (possibly $5HT_1$ receptors), there also appear to be differences in certain other 5HT receptor interactions (i.e., $5HT_2$ receptors [2, 20, 21, 30]).

The pattern of disruption in the FR-40 operant behavior by the hallucinogens (LSD, DMT, DOM, mescaline) is different than for most other psychoactive drug classes [28]. However, this pattern of a dose-related decrease in reinforcers coupled with an increase in pausing was also observed with non-hallucinogenic 5HT agonists (lisuride, quipazine, m-chlorophenylpiperazine, fenfluramine). The effects of all of these agents were antagonized by metergoline and pizotifen, which act at both $5HT_1$ and $5HT_2$ brain receptors [2, 9, 15, 18, 26, 27]. Cinanserin and pirenperone also effectively

antagonized the effects of the hallucinogens, but cinanserin potentiated while pirenperone caused little attenuation of the effects of lisuride. Cinanserin and pirenperone were very effective antagonists of quipazine, but the FR-40 and other behavioral effects of quipazine differ in a number of ways from those of the hallucinogenic agents, as described above.

These results, along with other reports [9,11], suggest that the hallucinogenic activity of LSD and mescaline-type drugs may relate to a particular spectrum of agonistic activity at both $5HT_1$ and $5HT_2$ receptors. Lisuride may fail to meet this criterion due to poor efficacy at the $5HT_2$ sites, and lower doses of quipazine may fail due to poor efficacy at the critical $5HT_1$ sites. It is true that drug receptor studies show that lisuride and quipazine bind to both $5HT_1$ and $5HT_2$ sites in brain [2, 10, 26, 27], but such studies do not readily characterize the ligand as an agonist, partial agonist or antagonist [14]. More work on the correlation between *in vitro* binding and functional activity of 5HT ligands [9] would be of great value in determining the significance of receptor binding studies.

The above hypothesis, though speculative, is amenable to testing. For example, subthreshold doses of either lisuride or quipazine would be expected to potentiate the disruption of FR-40 behavior by the hallucinogenic agents, and this in fact does occur ([8]; Mokler and Rech, unpublished observations). Interactions between lisuride and quipazine should also be examined. The availability of a selective $5HT_1$ antagonist would be useful for testing the hypothesis, as would the development of an effective and specific animal model for hallucinogenic drug action. We are currently exploring these possibilities.

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