5-HT Agonists as Psychoactive Drugs
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HALLUCINOGENIC 5-HYDROXYTRYPTAMINE AGONISTS CHARACTERIZED BY DISRUPTION OF OPERANT BEHAVIOR[1]

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INTRODUCTION

This article describes studies of the mechanism(s) of the more selective hallucinogenic drugs (sometimes called psychedelics or psychodysleptics) through their actions to disrupt operant behavioral patterns of rats. Although mankind has experienced and been fascinated with the effects of mind-altering plant substituents throughout the ages, concerted efforts for the scientific study of this type of agent began only about 50 years ago (Sankar, 1975). The development of animal models to simulate effects of lower doses of these drugs on the human brain has been hampered by the fact that the effects of these actions, though impressive, are largely subjective in nature. The overt toxic psychosis of large doses in man can more easily be mimicked by administering comparably large doses to various mammalian species (Davis et al., 1984; Sloviter et al., 1980). While some animal models relate to these large-dose effects, others (drug-discrimination, see Cunningham and Appel, this volume; FR-40 operant response disruption as presented here) have attempted to examine low-dose effects that have no appreciable influence on overt behavior. This latter strategy is based in part on 1) defining effects on brain mechanisms that would more likely relate to subjective effects of low doses in man, and 2) the likelihood that the lowest effective doses would manifest more selective (and thus hopefully more relevant) alterations in brain function.

The experimental approaches used to study the hallucinogenic drugs have been very diverse. Table 1 lists some key reports starting with the synthesis and description of human subjective effects of LSD by Albert Hofmann. Although the experimental methods and designs have varied widely, and in spite of the difficulties of identifying appropriate animal models, there appears to be considerable agreement in recent times that indolealkylamine and phenylalkylamine classes of hallucinogens act on brain 5-hydroxytryptamine (5-HT) receptors as agonists. However, a number of other drugs have been described as exerting agonistic effects at the various types of brain 5-HT receptors (5-HT_1, 5-HT_2 and autoreceptors), but are not hallucinogenic. A

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particular spectrum of interaction of the hallucinogens with central 5-HT receptors may be the solution to their peculiar activity. Thus, many laboratories, including ours, are attempting to define this pattern of activity on brain 5-HT mechanisms in the hope of discovering the neuronal/neurotransmitter correlates of the distinctive cognitive disturbances induced by these drugs.

Table 1

Milestones in Hallucinogenic Drug Research

1. **Hofmann:** Synthesis, first description of human effects of LSD, 1943.
2. **Gaddum; Woolley and Shaw:** LSD blocked peripheral 5-HT neurotransmitter function; similar mechanism proposed for CNS effects, 1953, 1954.
3. **Appel, Freedman and colleagues:** Operant behavior of rats disrupted in a distinctive pattern by indolealkylamine and phenalkylamine hallucinogens, 1960's.
4. **Aghajanian and coworkers:** LSD was a potent suppressor of 5-HT raphe cell discharge by agonistic action at autoreceptors, early 1970's.
5. **Jacobs and colleagues:** Autoreceptor activity of LSD was not sufficient to explain hallucinogenic behavioral effects, late 1970's.
6. **Domino and others:** Contrasted effects of deliriant hallucinogens (atropine-type, PCP) with those of the psychedelics, 1960's, 1970's.
7. **Hollister and others:** Clinical research; LSD, etc., induced hallucinations despite retained insight, 1950's, 1960's.
8. **Appel; Glennon; Jacobs; Rech:** Psychedelics acted as agonists at brain 5-HT receptors to alter behavioral responses, 1970's, 1980's.

METHODS

As stated above, the usual doses of hallucinogens of the LSD type when ingested by humans induce mainly subjective changes as the most prominent features. Therefore, an animal model for these more subtle aspects of behavior should avoid the use of larger doses that cause gross disturbances in autonomic and psychomotor functions, as well as obvious alterations in general behavioral demeanor. This is not to deny that the study of large-dose effects in experimental animals has a value; indeed they have aided in the understanding of overdose effects in man as well as offered clues to basic mechanisms of these classes of agents. Perhaps the most sensitive and elegant animal model is the drug discrimination paradigm as practiced by Appel (this volume), Rosecrans et al. (1978) and Glennon et al. (1986). One potential drawback of the drug discrimination paradigm is that, by definition, associative factors in cognitive functioning must be relatively intact for the subject to recognize the drug-induced cues as well as to

discriminate from or generalize to previously-experienced cues related to the effect of a psychoactive substance. Furthermore, this procedure requires many repetitions of the drugged state during performance of the behavior, which could induce certain types of tolerance or adaptation to some effects of the drug. We chose to study the pattern of disruption of the fixed ratio-40 (FR-40) schedule of operant responding in rats as a sort of middle ground (Rech et al., 1975; Rech and Commissaris, 1982; Rech and Mokler, 1986). That is, this test does quantify disruptive effects of the LSD-type of hallucinogen in doses that induce little or no change in grossly-observed home-cage behavior. It may, therefore, represent a model of cognitive distortions of considerable dimensions as experienced in humans who have ingested an LSD-like drug, but may still be in the range of "usual" doses and not constitute an overdose phenomenon.

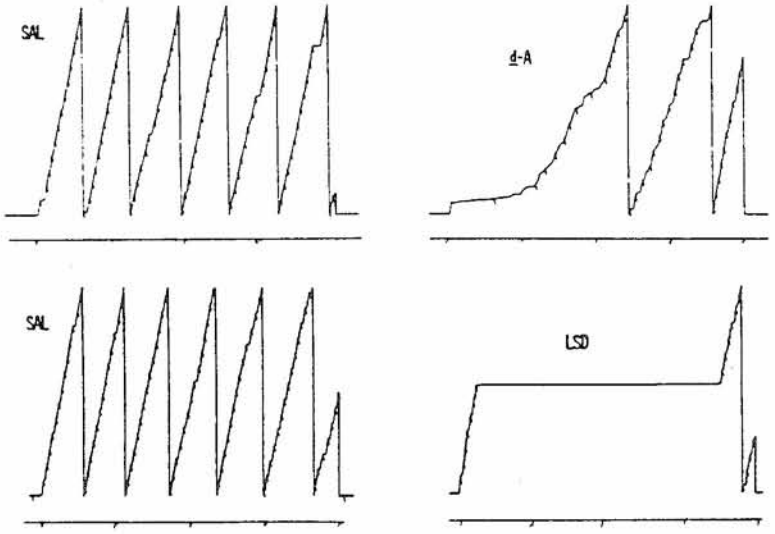

FIGURE 1. Cumulative recordings of FR-40 sessions. Top traces of each panel: lever presses deflect pen upward slightly (full excursion = 550 responses, triggering reset); oblique ticks on the trace signal completion of 40 responses and delivery of a reinforcer. Bottom traces of each panel: ticks mark off 10 min periods of the 40-min session. Left-hand panels illustrate control (saline injection) pattern in two different subjects. Right top panel indicates the effect of d-amphetamine (d-A), 1.0 mg/kg. Right bottom panel shows the effect of LSD, 100 µg/kg. Reprinted from Rech and Commissaris, 1982.

The subjects in the FR-40 studies were male Sprague-Dawley rats housed singly in temperature-controlled animal quarters with a 12-hour light cycle (lights on at 7 a.m.). The animals were maintained at approximately 80% of their free-feeding weight. They were trained in standard operant chambers containing a single lever, equipped with food

pellet dispensers, and enclosed in sound-attenuating boxes. After the subjects achieved asymptotic responding (near-continuous responding over a 40-minute daily session to earn approximately 80-100 pellets), the effects of drugs were determined on two parameters: 1) number of reinforcers obtained and 2) number of inter-response intervals greater than 10 seconds. The number of reinforcers earned is of course a reflection of the response rate (40 lever presses per pellet). We have given inter-response time periods greater than 10 seconds the designation "pauses". The 10-sec parameter was chosen since a small number of these pauses were present in control sessions but they increased dramatically after administering an hallucinogenic drug. We have found a reciprocal relationship between the decrease in reinforcers and the increase in pausing over the entire dose-response range for FR-40 disruption by the indolealkylamine and phenalkylamine hallucinogens. While many other classes of psychoactive agents (stimulants, barbiturates, neuroleptics) induce pausing in the FR-40 pattern, this occurs only at doses exceeding the ED_{50} for decreasing reinforcers (i.e., overall decrease in response rate). This phenomenon is illustrated with cumulative recordings of approximate ED_{50} doses of LSD and d-amphetamine (Fig. 1). The comparison of hallucinogens and non-hallucinogens for effects on FR-40 is shown in Table 2.

Table 2

Relationship Between Drug-induced Decrease in Reinforcers and Increases in Pause Intervals in the FR-40 Response Pattern

Drug and Dose	N	Percent of Control Reinforcers	Increase in Number of Pauses
Hallucinogens			
100 µg/kg LSD	8	44± 8*	94±13*
0.5 mg/kg DOM	8	45±11*	102±21*
1.8 mg/kg DMT	8	52±10*	72±14*
7.1 mg/kg mescaline	8	59± 6*	69± 6*
Non-Hallucinogens			
1.0 mg/kg d-amphetamine	8	54± 9*	18±16
25 mg/kg phenobarbital	8	63±11*	14±13
1.0 mg/kg chlorpromazine	7	67± 8*	17±10
30 mg/kg cocaine	4	46± 9*	27±21
200 µg (ICV) 6-OHDA	6	53±13*	25±17

Each value represents the mean ± S.E. percent of control reinforcers or change in pause intervals from control value. Modified from data presented in Commissaris et al., 1981e.

*$p < 0.05$, Student's t-test for paired values.

The neurotoxin 6-hydroxydopamine was administered intracerebroventricularly.

It is clear from the above that most classes of psychoactive agents studied decrease response rate in FR-40 over their lower dose ranges without significantly increasing pausing. The hallucinogenic agents represent exceptions in this regard but not the only ones. As will be apparent later, various drugs such as quipazine, lisuride and m-chlorophenylpiperazine (mCPP), non-hallucinogenic agents with 5-HT agonist activity, also demonstrate a reciprocal decrease in reinforcers and an increase in pausing over lower effective dose ranges.

A limited number of tests was performed in two other behaviors: (1) conditioned suppression of drinking (CSD) and (2) accommodated locomotor activity. In the former, rats were trained to drink their daily ration of water over a 10-min period in a Plexiglas® cage equipped with a drinking tube. After daily intake had stabilized, 7-sec tones were presented intermittently (variable interval - 21 sec). During the latter 5 sec of these 7-sec periods a small electrical current was applied to the drinking tube and the stainless steel floor of the cage. The subjects quickly learned to suppress drinking tube contact during the tone periods and concentrate their drinking in the silent periods. The number of shocks accepted in a daily session yielded the measure of punished responding while the amount of water ingested was taken as unpunished responding (negligible water was consumed during tone periods). This procedure was found to identify anxiolytic drug effects with a spectrum similar to that of the Geller-Seifter conflict test (Kilts et al., 1981). Furthermore, Schoenfeld (1976) used an acute-conflict version (Vogel-Beer test) of this procedure to determine the effects of LSD and mescaline. Consistent with an hypothesis that reduced activity of brain 5-HT neurons can interfere with conflict behavior, LSD and mescaline increased punished responding. Therefore, we tested the hallucinogens and compared their actions with anxiolytics and other agents to attempt to confirm these observations (Kilts et al., 1982; Commissaris et al., 1981b; Commissaris and Rech, 1982).

The accommodated locomotor activity measurement was developed in several forms some years ago by Stolk and Rech (1967) and Pirch and Rech (1968) to explore the behavioral effects of chronic reserpine in rats. Rats were placed in circular-runway cages fitted with photocells and contained in a dark, sound-attenuating enclosure (Rech and Heath, 1986). After 2 hours the subjects had habituated to a low level of activity. They were quickly removed, injected with drug vehicle and returned to the activity cage, with activity counts recorded for the next hour. Several serial tests on succeeding days demonstrated a consistent low level of counts, characteristic for each rat, following saline. On the day following the last saline test, a drug test day was introduced by substituting a dose of LSD, mescaline, lisuride, quipazine, or RU-24969 (5-HT agonists) for saline. The activity counts for each subject on this day were compared to those of the preceding saline day by Student's t-test for paired data. This procedure was repeated for other doses of the drug at 3-4 day intervals until a total dose-response analysis was completed. Several doses of each agent were repeated to confirm the consistency of the drug effect, and doses of quipazine which significantly altered accommodated locomotor activity were

tested again after pretreating with the non-selective 5-HT antagonist metergoline.

RESULTS

Neurotransmitter Depletion

Various pretreatments were administered to compromise the integrity of catecholamine or 5-HT brain pathways. α-Methyltyrosine (αMT) was injected i.p. in 50 or 100 mg/kg doses 40 min before testing drug effects on the FR-40. These doses of αMT effectively block the synthesis of brain catecholamines, but not 5-HT. αMT did not significantly alter FR-40 response patterns from control nor the disruptive effects of the hallucinogens (Mokler et al., 1982). p-Chlorophenylalanine (PCPA) was administered i.p. in 100 mg/kg doses for 3 days to rats that had shown reliable and significant pausing to LSD (50 μg/kg) and DOM (0.5 mg/kg). On the fourth day the hallucinogens were again tested and disruptive effects on FR-40 behavior were potentiated (Commissaris et al., 1980b; see also Appel et al., 1970). In separate subjects pretreated with PCPA the 5-HT concentration in various brain regions was depleted to 15-26% of control, while dopamine (DA) and norepinephrine (NE) remained at 73% or more of control values.

The neurotoxins 5,7-dihydroxytryptamine (5,7-DHT, lesions selectively brain 5-HT neurons) and 6-hydroxydopamine (6-OHDA, lesions selectively brain catecholamine neurons) were injected intraventricularly (ICV) or infused intracranially (IC) into rat brains by stereotaxic techniques (Table 3). 6-OHDA ICV was effective in depleting brain catecholamines to 6-24% of control in hypothalamus, neocortex, hippocampus, or striatum, but spared 5-HT levels in these regions to at least 70% of control. The opposite pattern was observed after ICV 5,7-DHT: the brain regions were reduced in 5-HT content to 13-34%, while catecholamines remained at 95% or more of control values. These neurochemical determinations were performed 3-1/2 or more months after infusion of the toxin, so it is quite likely that the extent of the lesions remained stable over the periods of drug testing.

The effect of LSD, DOM or mescaline on the FR-40 response pattern to increase pausing is compared for vehicle-infused and ICV 5,7-DHT-lesioned rats in Fig. 2A. For all three agents the dose-response curves for increasing pauses were significantly shifted to the left in subjects receiving the neurotoxin intraventricularly. When the disruptive pattern of d-amphetamine or phenobarbital was examined in these same subjects, no significant differences between the two groups were observed (not illustrated). In animals that received 6-OHDA ICV to lesion brain catecholamine neurons, no differences in the LSD or DOM disruption of FR-40 was noted for vehicle-treated vs. neurotoxin-treated rats, while the disruption of FR-40 by d-amphetamine was attenuated by the 6-OHDA pretreatment. Administration of 5,7-DHT IC into the medial forebrain bundle, Fig. 2B, potentiated FR-40 disruption by LSD, but less than after ICV 5,7-DHT; DOM effects were attenuated in these subjects, and mescaline effects were unchanged.

5,7-DHT infused into nucleus accumbens, septum or amygdala (Table 3) did not alter the FR-40 disruption by LSD, DOM or mescaline (not illustrated).

Table 3

Neurotoxins Infused into Brains of Rats Tested in the FR-40

Agent,* Route:	Stereotaxic Coordinates + A.P./Lat./Ver.	Neurotoxin Concentration and Rate	Brain Amines (Various Regions) Percent of Control
6-OHDA ICV	A6.0/1.5/+2.4	200 µg/10 µl, 5 µl/min	NE: 6-13% DA: 23-24% 5HT: 70-108%
5,7-DHT‡ ICV	A6.0/1.5/+2.4	180 µg/10 µl, 5 µl/min	NE: 97-125% DA: 95% 5HT: 13-34%
IC, MFB	A2.6/1.0/-3.0	6 µg/2 µl, 1 µl/min	NE: 90-111% DA: 120% 5HT: 48-81%
IC, NA	A9.4/0.8/-0.8	8 µg/2 µl, 1 µl/min	DA: 99-117% 5HT: 23%
IC, SEP	A8.2/0.0/+0.8	4 µg/2 µl, 1 µl/min	NE: 75-108% 5HT: 25-41%
IC, AM	A4.2/3.8/-3.0	4 µg/2 µl, 1 µl/min	Not Assayed

*Abbreviations: 6-OHDA = 6-hydroxydopamine; 5,7-DHT = 5,7-dihydroxytryptamine; ICV = intracerebroventricular; IC = intracranial; MFB = medial forebrain bundle; NA = nucleus accumbens; SEP = septum; AM = amygdala. Other than for the SEP, all IC infusions were bilateral. Data derived from Commissaris et al. 1980a, 1981c and d.

+Derived from Konig and Klippel, 1963, with corrections for size of subject.

‡Pargyline (40 mg/kg; 40 min pretreatment) and desipramine (25 mg/kg; 45 min pretreatment) were administered to potentiate and make more specific, respectively, the neurotoxicity of 5,7-DHT for 5-HT neurons.

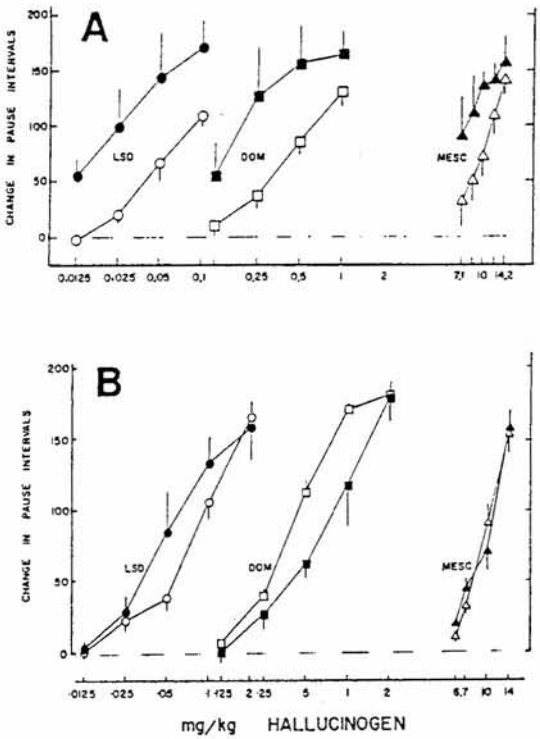

FIGURE 2. Dose-response patterns of LSD, DOM and mescaline (MESC) for FR-40 pausing in vehicle- (unfilled) or 5,7-DHT pretreated rats. The neurotoxin was infused intracerebroventricularly (ICV, from Commissaris et al., 1981c) in A and into the medial forebrain bundle (IC, from Commissaris et al., 1981d) in B. A: The pretreatment potentiated all 3 agents. B: The pretreatment potentiated LSD effects, attenuated DOM effects, and did not alter MESC effects.

Local Administration of Agonists

To explore further brain sites and receptor mechanisms involved in the FR-40 disruption by the hallucinogenic agents we implanted chronic cannulae into the lateral cerebral ventricle (ICV; Mokler and Rech, 1984) or 5-HT-relevant brain sites (IC; see Fig. 3) of rats trained in the FR-40 procedure (Mokler et al., 1986, 1987). The initial effort compared ip and ICV dose-response patterns of LSD, DOM, mescaline and lisuride to disrupt the FR-40 behavior. There was a small but significant decrease in the ICV ED_{50} dose of LSD to increase pause intervals as related to the ip dose (Table 4), and latency to the maximal effect was reduced from the second to the first 10-min period of the 40-min behavioral session. The effect by both routes had dissipated by

the end of the session. The ICV ED_{50} dose of DOM to increase pausing was almost one-third that of the ip dose, and the latency to maximal effect was reduced from the second or third period to the first 10-min period. Pausing generally remained significantly increased for the entire session after DOM by either route. Mescaline (effects not listed in Table 4) was much more potent to increase pausing by the ICV route as compared to the ip route. The mescaline ICV and ip ED_{50}s were 74 µg (38-109, 95% C.L.) and 2251 µg (1560-3142, 95% C.L.), respectively,

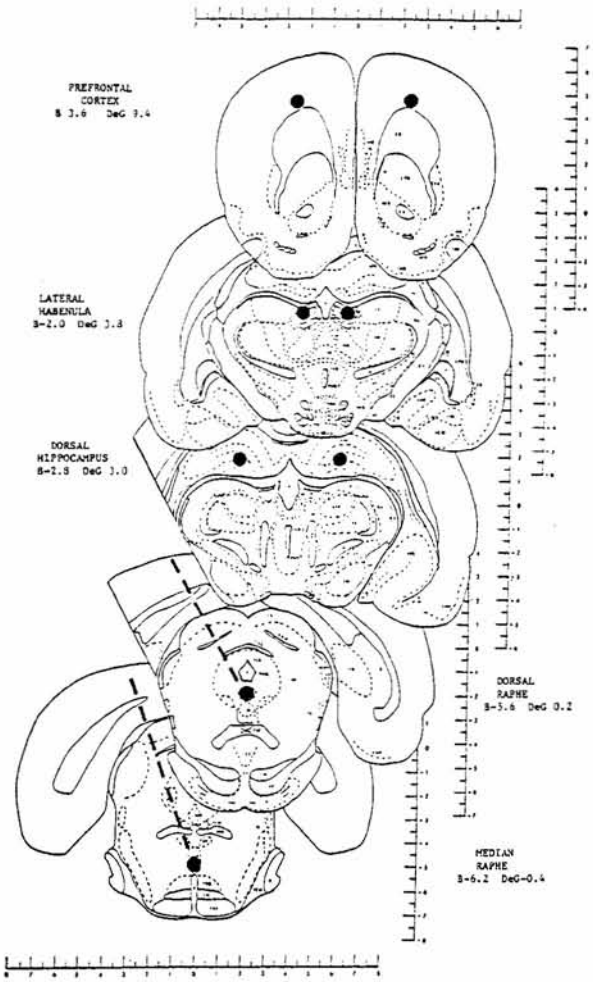

FIGURE 3. Sites of cannula placement, from Mokler et al., 1986. Single slanted cannulae placed in raphe nuclei. B = AP coord. from bregma, DeG = A.P. coord. from interaural zero.

for a 30-fold shift, but without systematic changes in time-course. The ip ED_{50} of lisuride to increase pauses (4 µg, 2-6 for 95% C.L.) was the same as the ICV ED_{50} (4 µg, 3-6 for 95% C.L.), without a systematic change in time-course. Thus, the only agent that showed a marked increase in potency when the route was changed from ip to ICV was mescaline, suggesting that the other agents tested enter the brain rapidly from the systemic circulation, a proposal supported by other work (Minnema et al., 1980; Stoll et al., 1975; see also Tilson and Sparber, 1972).

Table 4

ED_{50}s for Changes in Pause Intervals After LSD or DOM ip vs. ICV and IC

Route	LSD (µg)	DOM (µg)
ip	19 (15-24)*	153 (45-223)
ICV	15 (10-19)	58 (13-83)
IC - Dorsal Raphe	9 (2-20)	77 (60-117)
- Median Raphe	25 (21-28)	47 (0-95)
- Lateral Habenula	54 (29-249)	103 (29-208)
- Dorsal Hippocampus	23 (14-37)	114 (74-187)
- Prefrontal Cortex	13 (0-47)	92 (17-298)

*Values determined by probit analysis of dose-response patterns. Numbers in parentheses are 95 percent confidence limits. Table derived in part from Mokler and Rech, 1984, and Mokler et al., 1986, 1987.

When LSD was administered by IC infusion into the dorsal raphe nucleus (Table 4, Fig. 4), the dose-related reciprocal decrease in reinforcers and increase in pauses was retained, and the ED_{50} of 9 µg was significantly less than ED_{50}s for the ICV or ip routes. Infusion of LSD into the median raphe, lateral habenula or dorsal hippocampus resulted in decreased potency as compared to the ICV dose, while application to the prefrontal cortex resulted in the same potency range (13 vs. 15 µg). The IC administration of DOM into these brain sites did not induce the same pattern of potency ratios as did LSD. The ED_{50}s of DOM infused into the various sites were not statistically different from the ICV values. However, there was a trend for an increased potency in the median raphe and decreased potencies in the lateral habenula, dorsal hippocampus, and prefrontal cortex, related to the ICV ED_{50}. Figure 4 shows that the IC dose-response in the lateral habenula is complex, with a bimodal dose-response pattern. Actually, two separate ED_{50}s could be calculated for the low and the high dose ranges of DOM: 64 µg (20-120 µg range) and 176 µg (160-240 µg range).

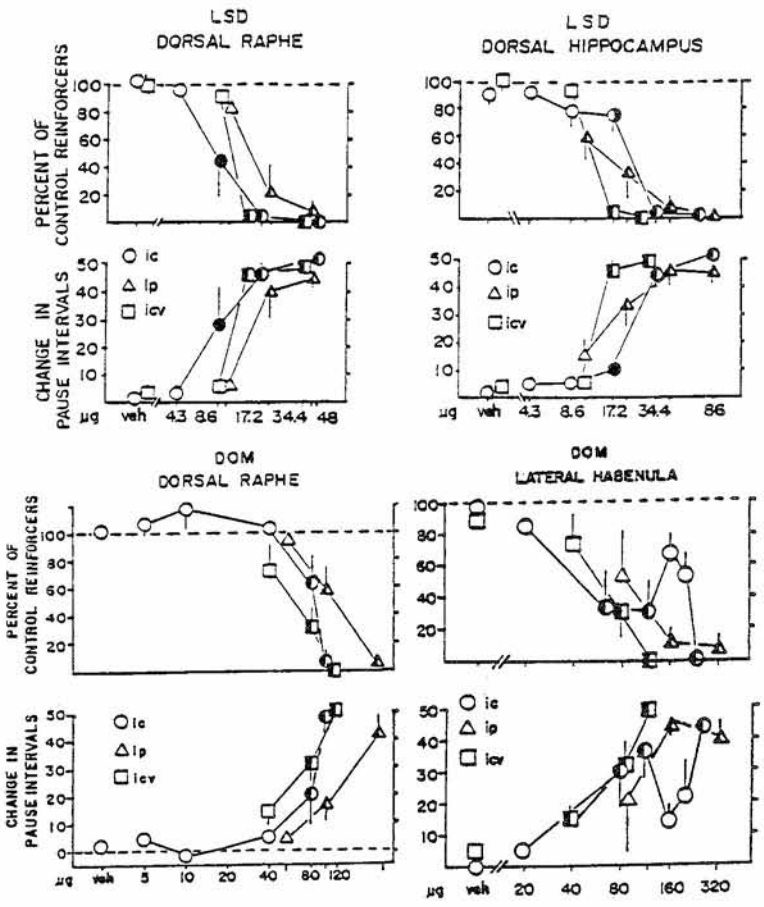

FIGURE 4. Dose-response patterns of LSD and DOM administered ip, ICV or IC into several brain areas to disrupt the ongoing FR-40 response pattern. Shading of left half of symbols signifies significant difference from control ($p < 0.05$, least significant difference test, one-way ANOVA); shading of right half of symbols indicates significant difference from IC drug effect (two-way ANOVA).

These results suggest that LSD effects may depend more critically on actions in the dorsal raphe and prefrontal cortex while the other sites are less active. DOM, however, may exert behavioral effects at the lowest dose by more ubiquitous activity throughout these brain structures, although the raphe nuclei and habenula may be slightly favored. We also tested for changes in the ip dose-response in cannulated rats. The ip ED_{50} of LSD for pausing was significantly reduced in subjects

cannulated in the dorsal raphe or prefrontal cortex, but not in animals cannulated ICV or in other areas. It appeared that only subjects cannulated in the lateral habenula showed increased sensitivity to ip DOM, but lack of uniformity in the ip doses tested in different groups thwarted this analysis. No trend for increased sensitivity to ip DOM was noted in rats cannulated in the dorsal raphe or prefrontal cortex. Thus far, mescaline has been tested IC in only one area, the prefrontal cortex. The ED_{50} for decreased reinforcers and increased pausing in FR-40 was significantly greater for infusion into prefrontal cortex as related to the ICV ED_{50} of mescaline (Heath et al., 1986). This is rather surprising, since the 5-HT_2 antagonist pirenperone was most effective against mescaline (Table 6), and 5-HT_2 receptors are relatively more dense in the prefrontal cortex as compared to other brain regions (Blackshear et al., 1981). However, the potencies of LSD and mescaline when placed into the prefrontal cortex are consistent with effects of 5,7-DHT lesions in the medial forebrain bundle (Fig. 2B), after which the FR-40 effects of LSD were enhanced but those of mescaline were unchanged.

5-HT Agonist-Antagonist Studies

When the non-selective 5-HT antagonist metergoline became available (courtesy of Farmitalia Carlo Erba), we tested this agent as an attenuator of the FR-40 disruption by the hallucinogens (Commissaris et al., 1981a), as seen in Fig. 5. The dose-response curves for LSD and DMT to decrease FR-40 reinforcers and increase pause intervals were significantly shifted to the right (about 3-fold) by pretreatment with metergoline (1 mg/kg), administered 3 hrs before. However, the attenuation of FR-40 effects of DOM or mescaline by metergoline pretreatment was much more dramatic, the dose shift being at least 10-fold. In contrast, neither the dose-response pattern of d-amphetamine nor that of phenobarbital to disrupt FR-40 was shifted significantly by pretreating with metergoline. The 5-HT agonists mCPP and fenfluramine altered the FR-40 response pattern with a reciprocal dose-related decrease in reinforcers and increase in pausing (as with the hallucinogens; not illustrated). Furthermore, pretreatment with metergoline blocked the disruption of operant behavior by these latter two agents. This work was extended (Mokler et al., 1983) to a comparison of metergoline, pizotifen and cinanserin for protection against the FR-40 effects of LSD, DOM, quipazine and lisuride. Table 5 shows that the non-selective 5-HT antagonist pizotifen was most effective in reversing LSD effects, both for decreased reinforcers and increased pausing, while metergoline and cinanserin were about equally effective against LSD. Metergoline is obviously the best antagonist of FR-40 effects of DOM, with pizotifen being considerably less effective and cinanserin being the weakest. Quipazine effects were blocked slightly better by metergoline as compared to pizotifen, with cinanserin being least effective. Lisuride was blocked modestly and about equally by metergoline and pizotifen. However, cinanserin pretreatment failed to block the increase in FR-40 pausing by lisuride and, in fact, potentiated the

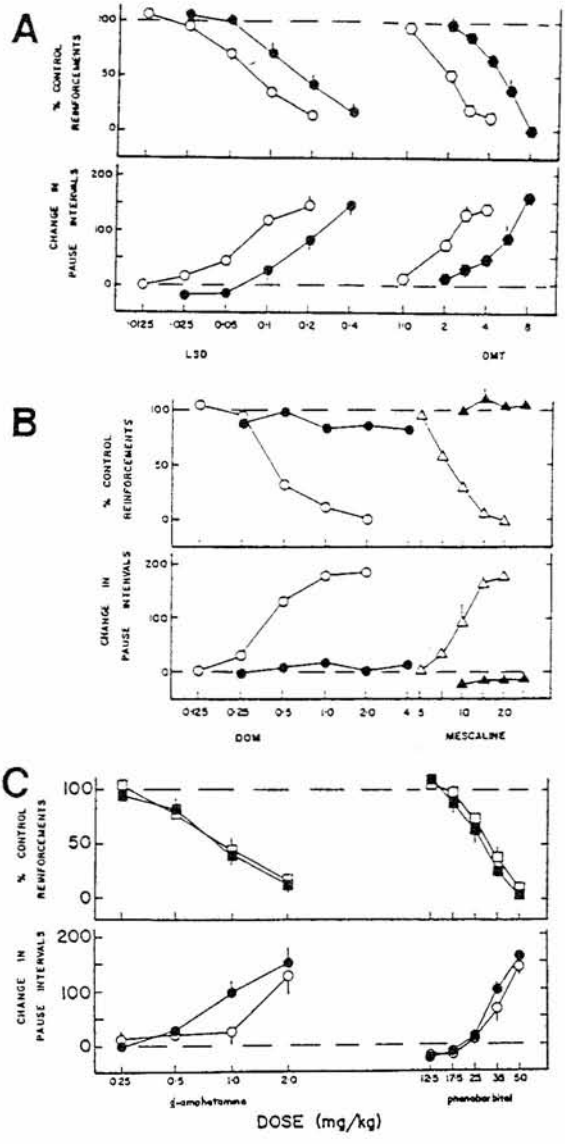

FIGURE 5. Extent of antagonism by metergoline of LSD, DMT (A), DOM, mescaline (B) and d-amphetamine and phenobarbital (C) effects on FR-40 reinforcements (upper panels) and pausing (lower panels). Unfilled symbols plot control dose-response, filled symbols depict dose-response in rats pretreated with metergoline (1 mg/kg 180 min before). Reprinted from Commissaris et al., 1981a.

decrease in reinforcers caused by lisuride. Thus, while each of these agonists appears to disrupt FR-40 operant patterns through a serotonergic mechanism, their interactions with the various 5-HT antagonists indicates that each agent's spectrum of activity appears to be somewhat distinctive.

Table 5

ED_{50} Values for Agonists Alone and in Combination with Antagonists

	LSD (µg/kg)	DOM (mg/kg)	QUIP (mg/kg)	LIS (µg/kg)
		Reinforcers		
Alone	**85** [52-122]*	**0.6** [0.3-2.9]	**1.6** [0.9-5.4]	**30** [25-36]
+1.0 Metergoline (180-min pretreatment)	**141** (1.7)+ [6-236]	**26.5** (44.2) [6.7-7.0E24]	**> 8.0**‡	**58** (1.9) [44-102]
+1.0 Pizotifen (40-min pretreatment)	**334** (3.9) [220-3931]	**3.2** (5.3) [1.1-16.4]	**> 8.0** ‡	**57** (1.9) [47-72]
+20 Cinanserin (80-min pretreatment)	**181** (2.1) [119-369]	**1.8** (3.0) [1.2-3.6]	**3.7** (2.3) [1.6-13.7]	**16** (0.5) [11-24]
		Pause Intervals		
Alone	**81** [68-98]	**0.6** [0.3-1.7]	**1.6** [1.0-3.1]	**31** [25-39]
+1.0 Metergoline	**195** (2.4) [132-281]	**> 8.0** ‡	**12.3** (7.7) [5.2-2.1E9]	**59** (1.9) [44-105]
+1.0 Pizotifen	**305** (3.8) [219-493]	**5.0** (8.3) [2.9-14.2]	**7.0** (4.4) [3.7-19.9]	**64** (2.1) [54-80]
+20 Cinanserin	**196** (24) [144-305]	**2.8** (4.7) [1.7-8.2]	**5.0** (3.1) [2.5-15.2]	**35** (1.1) [29-44]

ED_{50} values for FR-40 reinforcers and pause intervals after LSD, DOM, quipazine (QUIP) and lisuride (LIS), before and after pretreatment with 5-HT antagonists, as calculated by probit analysis (from Mokler et al., 1983).

*95% confidence limits.

+Ratio of $\frac{ED_{50}\text{ (agonist + antagonist)}}{ED_{50}\text{ (agonist)}}$

‡Estimation; probit analysis of dose-response curve indicates nonsignificant slope.

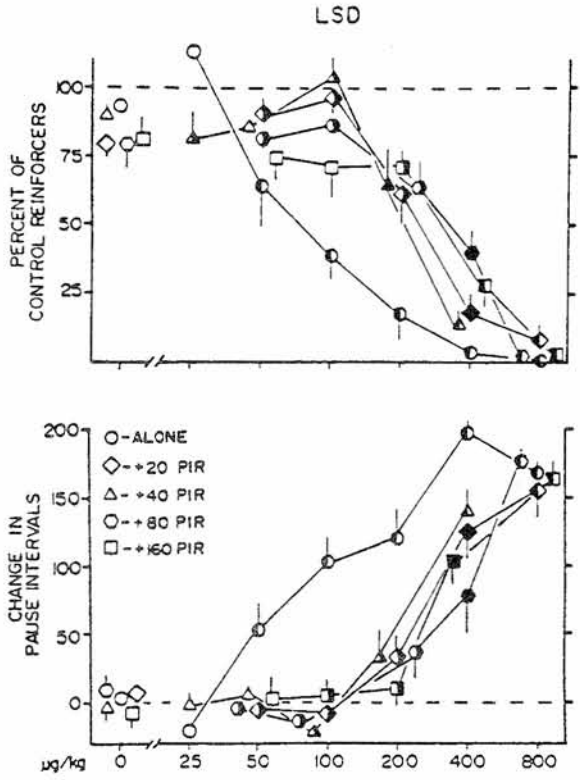

FIGURE 6. Effects of LSD on FR-40 responding alone or after pretreatment with various doses of pirenperone. Shading of left half of symbols = significant difference from control ($p < 0.05$, one-way ANOVA, least significant difference test). Shading of right half of symbols = significant difference from LSD alone ($p < 0.05$, two-way ANOVA, least significant difference test). Reprinted from Mokler et al., 1985.

When selective 5-HT_2 antagonists became available, Janssen Pharmaceutica, Inc., kindly furnished us a supply of pirenperone and ketanserin. We found pirenperone to be a very potent antagonist of FR-40 disruption by LSD as illustrated in Fig. 6. Comparison of antagonistic properties of pirenperone for the pause effects of LSD, DMT, DOM, mescaline, quipazine, and lisuride is shown in Table 6. The ED_{50} of LSD was increased by 3-fold after 20 µg/kg pirenperone, and only slightly increased beyond this by larger doses of the antagonist. On the other hand, DMT effects were not blocked maximally until preceded by 80 µg/kg pirenperone. DOM effects to increase pausing were reversed quite well by all doses of pirenperone tested, although

Table 6

ED_{50}s for Change in Pause Intervals for Agonists Alone and After Pirenperone

	Alone	+20 µg/kg PIR	+40 µg/kg	+80 µg/kg
LSD (µg/kg)	**103** [61-184]+	**307** (2.98)* [213-443]	**266** (2.58) [216-354]	**374** (3.63) [290-552]
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]
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]
Lisuride (µg/kg)	**27** [20-40]	**56** (2.07) [34-85]	**37** (1.37) [31-46]	**46** (1.70) [39-55]

ED_{50}s were determined by probit analysis. Data derived from Mokler et al., 1985.

$$*\text{Dose ratio} = \frac{ED_{50}\text{: agonist plus pirenperone}}{ED_{50}\text{: agonist alone}}$$

+95% confidence interval.

this antagonism was less dramatic than that involving DOM and metergoline (confer Table 5). The shift in the ED_{50} of mescaline to induce pausing was most dramatic after pirenperone (metergoline pretreatment had also markedly shifted the dose-response curve of mescaline, in Fig. 5), but required the largest dose of pirenperone (80 µg/kg) for the maximal effect. Thus, the optimal dose of pirenperone for antagonism varied independently of whether the hallucinogenic agent was an indolealkylamine or a phenalkylamine. Quipazine was not as well antagonized by pirenperone as it was by metergoline (confer Table 5) and it required the largest dose of the antagonist for maximal shift of the dose-response curve. Lisuride was the most potent drug to increase FR-40 pausing and it was the only agonist for which the dose-response pattern was not significantly shifted by pretreating with pirenperone. Assuming that pirenperone is acting as a specific $5\text{-}HT_2$ antagonist, lisuride then would appear to exert little of its disruptive influence by acting on brain $5\text{-}HT_2$ receptors. All of the other agonists

would appear to have a significant activity on 5-HT_2 receptors in disturbing FR-40 responding, this component being greatest for mescaline, somewhat less for DOM and quipazine, and least for LSD and DMT. Nevertheless, with reference to the indolealkylamine hallucinogens, pirenperone was at least as effective an antagonist of operant behavioral disruption as was metergoline (compare shifts in dose-response patterns of LSD and DMT in Table 6, 3-fold or more, with those in Fig. 5A, between 2- and 3-fold). In preliminary studies with ketanserin as an antagonist of the FR-40 disruptive effects of LSD, DOM, quipazine and lisuride, essentially the same patterns of interaction were noted as after pretreatment with pirenperone.

Table 7

Effects of 5-HT Antagonists on FR-40 Responding

Treatment	% Control Reinforcers*	Change in Pause Intervals*
Metergoline, 1 mg/kg, 180 min before	104+4	-18+3‡
Metergoline+ 0.1 mg/kg, 180 min before	111+5 ‡	-15+3‡
Metergoline+ 1 mg/kg, 180 min before	108+6 ‡	-19+4‡
Pizotifen 1 mg/kg, 40 min before	105+3	-14+4‡
Cinanserin 20 mg/kg, 80 min before	95+2 ‡	-12+4‡
Pirenperone 20 µg/kg, 40 min before	98+4	0+4
Pirenperone 80 µg/kg, 40 min before	93+4	-1+5

*Mean ± S.E.M. for 8-24 rats per group.

+Reinforcement data for this group was normalized by square root transformation prior to statistical analysis.

‡$p < 0.05$, Student's t-test for paired values. This data is derived in part from Commissaris et al., 1981a,e; Commissaris and Rech, 1981; and Mokler et al., 1983, 1985.

Although the effects of optimal doses of the various 5-HT antagonists alone on FR-40 responding were subtle, there were significant changes as indicated in Table 7. Metergoline, pizotifen and cinanserin all induced a significant decrease in pausing from baseline control levels, while pirenperone did not. This suggests that 5-HT_1 receptor antagonism attenuates the normal rate of FR-40 pausing. Analyzing the raw data for reinforcers, there was a trend for an increase after metergoline or pizotifen but without significance. In two groups where the data for reinforcers was normalized by square root transformation, metergoline (0.1 or 1.0 mg/kg) increased significantly the number of reinforcers over control values. However, cinanserin caused a decrease in reinforcers at 20 mg/kg (at slightly larger doses or in other groups this decrease was more prominent than shown in Table 7). This may relate to a weak partial agonist effect of cinanserin at 5-HT_1 receptors, which could also explain the greater reduction in reinforcers by lisuride in rats pretreated with cinanserin (see again Table 5). Table 7 also shows that pirenperone has nonsignificant effects on either reinforcers or pause intervals, which could be related to its 5-HT_2 receptor selectivity.

Several other drug interactions that were explored involved pretreatment with neuroleptics (chlorpromazine, haloperidol) or d-amphetamine in subthreshold doses. These pretreatments did not affect dose-response patterns for LSD or DOM, while pretreatment with subthreshold doses of LSD, mescaline, mCPP or quipazine potentiated FR-40 pausing by DOM (Commissaris et al., 1981e).

Opioid-Hallucinogen Interactions

Other evidence that various 5-HT agonists act on somewhat dissimilar brain mechanisms derives from their interactions with opioids. Domino and colleagues first described enhancement of LSD or DMT disruption of a fixed ratio schedule in rats by pretreating the subjects with naloxone (Ruffing et al., 1979). We showed that naloxone also potentiated the FR-40 disruption by mescaline (Commissaris et al., 1980c) and DOM, as well as confirming the interaction of naloxone with LSD (Mokler et al., 1984). Figure 7 illustrates the interaction between naloxone and mescaline or LSD. In neither case was there a parallel shift in the dose-response of the hallucinogens as noted earlier with potentiation after 5,7-DHT (confer Fig. 2A). The naloxone pretreatment enhanced effects of high doses but not low doses of mescaline, while the opposite pattern was observed for the interaction between naloxone and LSD. The interaction of DOM with naloxone (not illustrated in Fig. 7) also resulted in enhanced pausing at low but not high doses of the hallucinogen. Figure 7A illustrates that the optimal dose of naloxone for these interactions was 4 mg/kg, with doses of 1 mg/kg or less having little effect. These results suggest that opioid receptors other than mu are involved since 4 mg/kg of naloxone is much greater than required to antagonize at the mu receptor (0.1-0.5 mg/kg). However, the 4 mg/kg dose of naloxone would be reasonable if delta receptors were involved. This speculation gains support from the

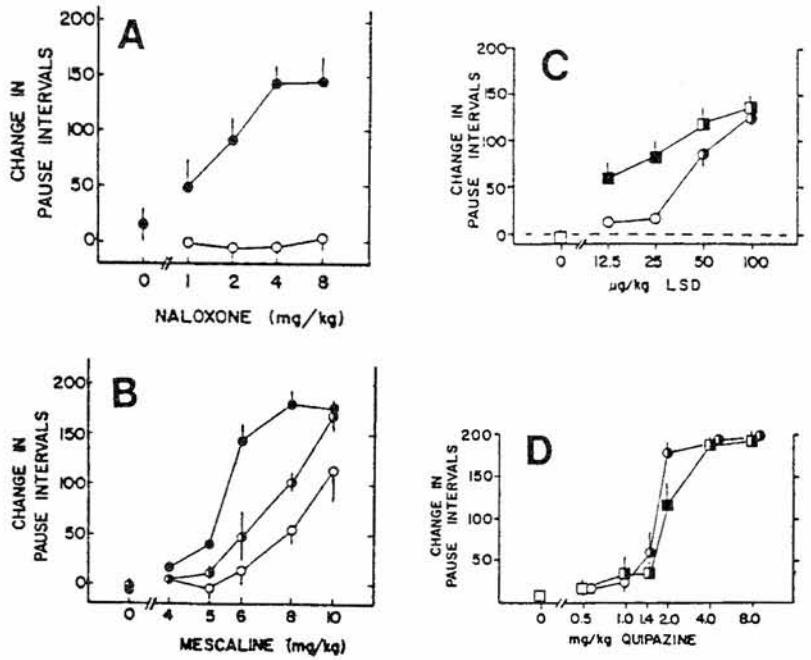

FIGURE 7. Interaction of naloxone with mescaline, LSD or quipazine on FR-40 pausing. A: dose-response of naloxone alone (open circles) or in combination with 6 mg/kg mescaline (filled circles). B: dose-response of mescaline alone to increase pausing (open circles) or after pretreatment with 1.0 (half-filled circles) or 4.0 (filled circles) mg/kg naloxone. C: dose-response of LSD alone (circles) or in combination with 4 mg/kg naloxone (squares). D: dose-response of quipazine alone (circles) or in combination with 4 mg/kg naloxone (squares). For C and D: shading on right-half of symbols = significant difference from control; shading on left-hand of squares = significant difference from LSD alone. Reprinted from Commissaris et al., 1980c, and Mokler et al., 1984.

observations of Ruffing and Domino (1981, 1983) that not only morphine but also synthetic metenkephalin peptide analogs attenuate the disruption of fixed-ratio operant behavior by LSD or DMT (we confirmed the attenuating effects of morphine, Rech et al., unpublished observations). It is unlikely that naloxone was acting at kappa receptors to enhance the effects of the hallucinogens, since naloxone actually attenuates the FR-40 disruption induced by kappa agonists (cyclazocine, ethylketocyclazine and U-50,488; Henck et al., 1983; Rech et al., 1984; Henck and Rech, 1984). The disruption of FR-40 responding by the kappa agonists is also attenuated to some degree by pretreatment with

metergoline, implicating an influence via 5-HT mechanisms. Quipazine differs in its operant behavioral effects from the hallucinogens in that naloxone pretreatment slightly attenuates its disruptive pattern rather than enhancing it (Fig. 7D). Quipazine may act on FR-40 by suppressing appetite since effective doses are in the same range, but this is not true for cyclazocine (Henck et al., 1985) or for LSD or mescaline (Rech, unpublished observations). These and other opioid interactions on FR-40 response patterns are summarized in Table 8.

Table 8

Summary of Opioid-Hallucinogen Interactions

1. Naloxone potentiates FR-40 disruption by hallucinogens while morphine attenuates it (stabilizing modulations by endorphins?).
2. Kappa agonists disrupt FR-40 with the hallucinogenic pattern; partly antagonized by naloxone or metergoline pretreatment (kappa and 5-HT destabilizing effects?).
3. SKF-10,047 disrupts FR-40 with the hallucinogenic pattern; little attenuation by naloxone or metergoline pretreatment (direct sigma receptor activity resistant to naloxone and bypassing 5-HT mechanisms?).
4. Quipazine disrupts FR-40 with the hallucinogenic pattern; well antagonized by metergoline and somewhat antagonized by naloxone (5-HT-opioid interactions on appetite controls?).

Tolerance, Cross-tolerance Studies

In past studies (Rech et al., 1975) we established the development of tolerance and cross-tolerance patterns for FR-40 disruption by LSD, DMT, DOM, mescaline and psilocybin. There was two-way cross-tolerance demonstrated among these agents for many pairs, although DOM demonstrated only one-way cross-tolerance (the LSD or mescaline effect was cross-tolerant in rats made tolerant to chronic DOM, but not vice versa) and some other combinations showed incomplete tolerance or cross-tolerance (see also Appel and Freedman, 1968, and Winter, 1971). These results suggested some but far from complete commonalities in the mechanisms of action of the various hallucinogenic agents. We also indicated in this earlier work that the 5-HT antagonist cinanserin attenuated FR-30 disruption by LSD, DMT, DOM, mescaline, and psilocybin in a dose (10 mg/kg) that did not reverse the FR-30 rate decrease induced by d-amphetamine or chlorpromazine. At that time we had not developed the method of quantifying pauses (Commissaris et al., 1980a,b), so that this more selective measure of effects of hallucinogens was not included. In the currently reviewed studies the quantification of FR-40 pausing was very useful in developing dose-response characteristics not only of the hallucinogens, but also of other 5-HT agonists as well. Furthermore, subtle influences of 5-HT anta

gonists were demonstrated with the measurement of pausing, as reviewed earlier (see Table 7).

Table 9

Extent of Cross-Tolerance Between Hallucinogenic and Non-Hallucinogenic 5-HT Agonists for Increase in FR-40 Pausing

LSD Test Dose Effect		Lisuride Test Dose Effect	
Initial:	49±12*	Initial:	57±19
After Chronic LSD:	8±6+	After Chronic LSD:	65±30
Mescaline Test Dose Effect		**Quipazine Test Dose Effect**	
Initial:	96±10	Initial:	68±19
After Chronic Mescaline:	36±8+	After Chronic Mescaline:	64±19

LSD test dose = 37.5 µg/kg; LSD chronic dosing = 150 µg/kg/day x 12. Mescaline test dose = 10 mg/kg; Mescaline chronic dosing = 14 mg/kg/day x 10. Lisuride test dose = 20 µg/kg. Quipazine test dose = 1.5 mg/kg.

*Values are increases in pause intervals over baseline control ± S.E.

+Significantly different from initial deficit, $p < 0.05$.

In recent studies, we (Mokler and Rech, unpublished work) tested the possibility of cross-tolerance between LSD and lisuride and between mescaline and quipazine for increasing pauses in the FR-40, as indicated in Table 9. LSD (37.5 µg/kg) and lisuride (20 µg/kg) initially caused a significant increase in the number of pauses during a 40-min session. Subsequently, these rats were treated with 150 µg/kg of LSD for 12 days, but FR-40 was not tested under the drug effect at this time. Then LSD (37.5 µg/kg) and lisuride (20 µg/kg) test doses were repeated. Prominent tolerance occurred for LSD disruption, but no cross-tolerance to the effect of lisuride was observed. A similar design was followed to test for tolerance to mescaline (10 mg/kg test dose) and cross-tolerance to quipazine (1.5 mg/kg test dose), with chronic dosing of 14 mg/kg mescaline per day for 10 days. Again, tolerance was observed for effects of mescaline but no cross-tolerance to quipazine disruption was noted. Therefore, despite the fact that LSD and lisuride show similar patterns in FR-40 disruption and attenuating patterns of 5-HT antagonists (Table 5), while mescaline and quipazine also manifest similar patterns in this regard, lisuride must act by a somewhat different mechanism than LSD and quipazine cannot be identical in mechanism to mescaline.

Effects on Other Behaviors

Schoenfeld (1976) has presented evidence for disinhibitory effects of LSD and mescaline on punished responses in an acute conflict procedure based on drinking behavior (see Methods). We examined the effects of LSD and DOM, among other agents, on a conditioned conflict paradigm involving suppression of drinking behavior (Commissaris et al., 1981b; Commissaris and Rech, 1982). Diazepam, pentobarbital and methaqualone caused prominent increases in punished responding in doses having little effect on unpunished behavior. LSD and DOM produced significant though modest increases in punished responses over a narrow dose range, with larger doses decreasing punished and unpunished responding. ICV 5,7-DHT or metergoline pretreatment did not alter the release of punished behavior by diazepam, pentobarbital or methaqualone but these pretreatments attenuated the small increases in punished behavior by LSD and DOM. Metergoline also reversed the depression of unpunished responses by larger doses of the hallucinogens. Quipazine did not increase punished responding but dose-relatedly depressed unpunished behavior (0.5-4 mg/kg); metergoline markedly antagonized the quipazine depression. Therefore, the hallucinogens can exert a modest anticonflict effect which appears to be mediated via brain 5-HT mechanisms, but which differs from the antipunishment mechanisms of classical anxiolytic agents. Quipazine differed from the hallucinogens in having no anticonflict activity, although quipazine depression of unpunished responses appears to involve 5-HT mechanisms. Fenfluramine (an indirect 5-HT agonist) and mCPP (a 5-HT_{1B} agonist) were ineffective in releasing punished responding (Kilts et al., 1982), as was RU-24969, a putative selective 5-HT_{1B} agonist (Heath and Rech, unpublished results). We have found modest anticonflict activity with buspirone (McCloskey et al., 1987; Heath and Rech, unpublished results), which may act as a 5-HT_{1A} agonist (Cunningham and Appel, this volume; Glennon, this volume). It may be that the weak anticonflict activity of the hallucinogens relates to a 5-HT_{1A} component.

To further explore the disinhibitory effects of the hallucinogens, we examined their influence on accommodated locomotor activity (Rech and Heath, 1986; see Methods). LSD and mescaline showed trends for increasing or decreasing this habituated activity at various doses (Fig. 8), but the responses were so variable as to preclude a significant effect at any dose, even with the use of a paired analysis. On the other hand, several doses of lisuride decreased, while several doses of quipazine increased activity counts. RU-24969 showed a biphasic effect: reduced counts at a low dose but increased counts at higher doses. The data illustrated in Fig. 8 again shows prominent differences in the behavioral effects of hallucinogenic and non-hallucinogenic 5-HT agonists. The lack of consistent stimulation or depression with LSD and mescaline may relate to a broader spectrum of activity at both 5-HT_1 and 5-HT_2 receptors, whereas lisuride, quipazine and RU-24969 interact with a more restricted variety of receptors. It seems likely that the motor activity changes after quipazine, at least,

were related to 5-HT agonistic effects since metergoline pretreatment before selected doses attenuated the effects of this agent on accommodated locomotor activity (not illustrated).

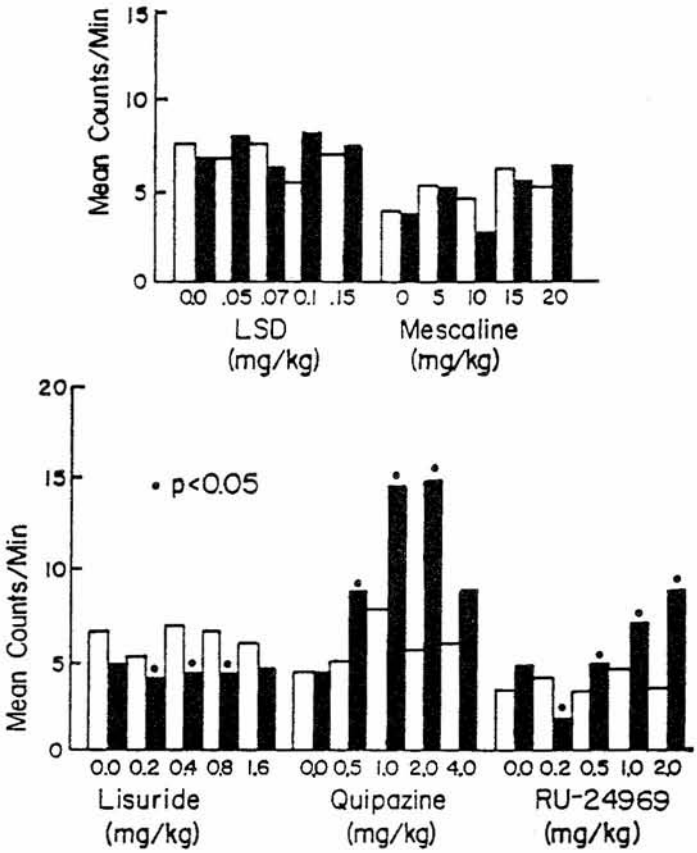

FIGURE 8. Effects of hallucinogenic and non-hallucinogenic 5-HT agonists on accommodated locomotor activity. Activity after each test dose (filled bars) was compared by a paired t-test to the preceding day's activity score following vehicle injection (unfilled bars). The dose-response pattern of each drug was analyzed in a separate group of rats. Data from Rech and Heath, 1986.

DISCUSSION AND CONCLUSIONS

The Introduction reviewed earlier studies of indolealkylamine and phenalkylamine hallucinogens that suggested that their behavioral effects relate to actions at brain 5-HT receptors. Nevertheless, these agents also affect dopaminergic mechanisms to some degree, which had led to proposals that actions involving the neurotransmitter dopamine

were implicated in hallucinatory effects in a primary way (Brawley and Duffield, 1972; Jacobs, 1978). At least with reference to the disruption of fixed-ratio operant behavior, hallucinatory agents of the indolealkylamine and phenalkylamine types appear to act mainly through 5-HT mechanisms. Neurotoxic lesions of 5-HT but not catecholaminergic neurons potentiated the FR-40 disruption by the halluciongens. Inhibition of the synthesis of 5-HT but not that of catecholamines influenced the dose-response patterns of LSD and DOM on FR-40 behavior. 5-HT antagonists but not neuroleptics attenuated the effects of the hallucinogens, and subthreshold doses of 5-HT agonists but not those of dopaminergic agents potentiated the FR-40 effects of hallucinogens.

Results from the lesion studies and intracranial infusions of hallucinogens suggest that these agents act at multiple brain sites with little dose differential and, except for mescaline, very rapidly diffuse into the brain from the systemic circulation. LSD and DOM, at least, appear to exert effects at various brain 5-HT sites with a somewhat different spectrum of sensitivities. Co-administration of the hallucinogens or non-hallucinogenic 5-HT agonists (lisuride or quipazine) with various 5-HT antagonists showed differences in susceptibility to attenuation of FR-40 disruptive effects. The non-selective blocker metergoline very dramatically antagonized the effects of DOM, mescaline and quipazine, but was much less impressive against the indolealkylamines. The non-selective 5-HT antagonist pizotifen was relatively more effective against the indolealkylamines, although about equal to metergoline in blocking the effective of lisuride. Cinanserin was about equally effective against all agonists except lisuride, which effects it actually potentiated. The 5-HT_2 receptor-selective antagonist pirenperone was most dramatic in blocking the effects of mescaline and less prominent in interacting with DOM and quipazine. The indolealkylamines were blocked less well by pirenperone but still very effectively compared to the interaction of LSD or DMT with metergoline. The dose-response pattern of lisuride for FR-40 disruption was not significantly shifted by pirenperone.

It is difficult to resolve the above interactions into a comprehensive theory relating to the specific 5-HT receptors that are most influenced by each of the agonists. Mescaline appeared to exert the most effect via 5-HT_2 mechanisms, while lisuride exerts little or no effect through these receptors. If lisuride is a 5-HT_{1A} agonist as suggested by Cunningham and Appel (this volume) and others (Hoyer, 1987), an enhanced effect after cinanserin may indicate that this antagonist has partial agonist activity at 5-HT_{1A} receptors (see also the discussion below on antagonist effects alone and relating to conflict behavior). Pizotifen may be relatively most effective against the indolealkylamines by virtue of a greater efficacy in blocking some 5-HT_1 sites. With regard to the relative antagonist efficacy of metergoline, LSD and DMT fall in one group, while DOM, mescaline and quipazine fit another. But pirenperone, while blocking mescaline extremely well, is considerably less effective against DOM and quipazine when compared to the antagonist effects of metergoline. This suggests that DOM and quipazine disrupt FR-40 responding by acting, in

part, presumably indirectly, on 5-HT_1 mechanisms. Other investigators have considered the behavioral effects of quipazine to be due predominantly to 5-HT_2 agonistic activity (Cunningham and Appel, this volume; Friedman et al., 1984).

The absolute extent of shift in the $ED_{50's}$ for disruption of FR-40 by LSD, DMT and mescaline was as great or greater with the antagonist pirenperone as with any other antagonist. Thus, it is tempting to equate the behavioral effects of the hallucinogens with their 5-HT_2 receptor activity, as has been suggested by other investigators (Appel and Rosecrans, 1984; Heym et al., 1984; Glennon et al., 1986). However, this would not explain the greater sensitivity of DOM to metergoline than to pirenperone, unless one invoked a concept of multiple sensitivities among various 5-HT_2 receptors. There is not a great difference among 5-HT antagonists in their affinity for the 5-HT_2 receptor (Leysen et al., 1981). If it were established that these hallucinogens exerted their behavioral effects by an agonist activity at only one type of 5-HT receptor, the 5-HT_2 type would seem to be the favorite. However, the experimental findings can also be explained as drug agonist effects at multiple receptors, if each receptor activity is necessary but neither is sufficient alone to induce the characteristic changes in behavior. An invaluable tool to test this hypothesis would be the use of a selective 5-HT_1 antagonist, for which a paucity of candidates are available at this time (see Gudelsky et al., this volume).

The subtle effects of 5-HT antagonists alone (Table 7) are of interest in exploring 5-HT influences on FR-40 operant behavior. The non-selective agents metergoline, pizotifen and cinanserin reduced pause intervals significantly from baseline control values, while the selective 5-HT_2 antagonist pirenperone did not (ketanserin was also ineffective in this regard). This reduction in pausing may therefore relate to an interference with baseline activity in brain 5-HT_1 mechanisms. Metergoline and pizotifen increased total responses (reinforcers earned, when scores were normalized), while cinanserin decreased overall responses. Cinanserin may reduce total responses by a partial agonist effect at 5-HT_{1A} receptors, which may also explain potentiation of the rate-reducing effects of lisuride (Table 5).

The enhanced pausing by the hallucinogens in rats pretreated with naloxone may reflect brain endorphin systems that exert an inhibitory modulation on the hallucinatory mechanisms. This proposal is supported by the protective effect against the hallucinogenic drug effects by morphine and enkephalins. Since the shifts in the dose-reponse patterns after naloxone pretreatment were non-parallel (Figure 7), these are probably indirect modulatory influences of opioid receptors on the pertinent 5-HT mechanisms. The FR-40 disruption of quipazine was attenuated by naloxone pretreatment rather than enhanced, suggesting that quipazine affects FR-40 responding by acting on somewhat different 5-HT systems than do the hallucinogenic drugs. The dose-range of quipazine to reduce free-feeding is in the same range as that disrupting FR-40 (Henck et al., 1985), but not in the case of cyclazocine, LSD or mescaline. Therefore, quipazine may attenuate FR-40 responding by activating 5-HT satiating systems at appetitive hypothalamic centers

for food, whereas the hallucinogenic agents appear to disrupt the FR-40 reponse pattern by distorting cognitive processing in the forebrain that relates to associative functions.

As indicated earlier, tolerance and cross-tolerance to the disruption of fixed-ratio operant behavior induced by indolealkylamine and phenalkylamine hallucinogens is well established. Since rats tolerant to the pause-inducing effects of LSD showed no cross-tolerance to the effect of lisuride (Table 9), these agents must disrupt FR-40 by quite different mechanisms. Likewise, rats tolerant to mescaline demonstrated on cross-tolerance to quipazine. The non-hallucinogenic 5-HT agonists presumably act on a different spectrum of 5-HT receptors than LSD and mescaline, even though the same pattern of FR-40 disruption was observed for all four agents.

The modest anticonflict effect of the hallucinogens may reside in a 5-HT_{1A} receptor activity (see Cunningham and Appel, this volume, and earlier text). Cinanserin, proposed earlier to have partial agonist activity at 5-HT_1 receptors, had appreciable anticonflict activity in several paradigms (Kilts et al., 1982; Geller et al., 1974), although this required a rather large dose to effect. Quipazine failed to release punishment-suppressed responding, although the drug depressed punished and unpunished responding, which effects were antagonized by metergoline. Quipazine may have too weak a 5-HT_{1A} influence to exert anticonflict activity.

The effects of the hallucinogens, lisuride, and quipazine on accommodated locomotor activity may also relate to the spectrum of 5-HT receptor types activated in brain regions controlling psychomotor functions (Figure 8). Lisuride only decreased motor counts, perhaps due to agonist activity mainly on 5-HT_1 receptors. Quipazine only increased counts, presumably relating to a predominance of 5-HT_2 receptors in the brain regions implicated. LSD and mescaline, while showing trends at some doses to increase or decrease motor activity, never induced a significant increase or decrease in counts. Large doses of some hallucinogens as well as various treatments that cause prominent increases of activity in brain 5-HT systems induce aberrant motor responses in rats. Some of these manifestations appear to relate to 5-HT_2 receptors, while others derive from activity at 5-HT_1 receptors (Lucki et al., 1984). In our measure of accommodated locomotor activity, the complex of effects of the hallucinogens on various brain 5-HT mechanisms affecting orienting psychomotor activity may provoke both excitatory and inhibitory components that tend to cancel one another out, resulting in no net change in counts.

In summary, the hallucinogens appear to be agonists at both 5-HT_1 and 5-HT_2 receptors. The spectrum and/or site of 5-HT agonist activity of non-hallucinogenic agents such as lisuride and quipazine probably differ from the hallucinogens in important particulars. The disruption of FR-40 operant behavior by relatively low doses of indolealkylamine and phenalkylamine hallucinogenic agents most likely involves multiple 5-HT sites in brain systems controlling associative functions. Agonist activity at 5-HT_1 or 5-HT_2 receptor types may be necessary but not sufficient to affect the operant behavioral disturb

ance, so that both types of receptor activation (varying in degree with the particular agent) are required for these hallucinogenic drugs to induce their typical alteration of the FR-40 response pattern.

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