0022-3565/81/2191-0170$02.00/0
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
Vol. 219, No. 1

Printed in U.S.A.

# Differential Antagonism by Metergoline of the Behavioral Effects of Indolealkylamine and Phenethylamine Hallucinogens in the Rat[1]

R. L. COMMISSARIS,[2,3] W. H. LYNESS,[4] K. E. MOORE and R. H. RECH
*Department of Pharmacology and Toxicology, Michigan State University, East Lansing, Michigan*
Accepted for publication July 20, 1981

## ABSTRACT

**Commissaris, R. L., W. H. Lyness, K. E. Moore and R. H. Rech:** *Differential antagonism by metergoline of the behavioral effects of indolealkylamine and phenethylamine hallucinogens in the rat.* J. Pharmacol. Exp. Ther. **219:** 170–174, 1981.

The effects of metergoline were examined on the behavioral disruption produced by hallucinogens of the indolealkylamine [*d*-lysergic acid diethylamine and N,N-dimethyltryptamine] and the phenethylamine [2,5-dimethoxy-4-methylamphetamine and mescaline] classes. Food-deprived male rats were trained to press a bar on a fixed-ratio 40 operant schedule of food presentation. Administration of the hallucinogens immediately before the start of the session resulted in a dose-dependent cessation of responding (*i.e.*, an increase in "pausing") for some period of the 40-min test session. Administration of *d*-amphetamine or phenobarbital produced slow and erratic intrasession response rates not characterized by pausing, except at the highest doses.Metergoline (1 mg/kg, 180 min before the start of the fixed-ratio 40 session) antagonized the pause-producing effects of all four hallucinogens, although the characteristics of this blockade were different for the indolealkylamine and the phenethylamine classes. The metergoline treatment employed in this experiment shifted the dose-response patterns of the indolealkylamines to the right, whereas the antagonist completely blocked the disruptive effects of the phenethylamines at all doses tested. The behaviorally disruptive effects of *d*-amphetamine and phenobarbital, in contrast, were not altered by metergoline pretreatment. These data support the hypothesis that 5-hydroxytryptamine neuronal systems are involved in the behavioral effects of the hallucinogens, but suggest that there are differences in the mechanisms by which the phenethylamine and indolealkylamine hallucinogens interfere with these neurons.

Although hallucinogens can be divided into phenethylamine and indolealkylamine classes on the basis of their chemical structures, examples of both classes appear to produce many of their behavioral effects through interactions with 5-HT neuronal systems. Andén *et al.* (1968, 1974) have shown that the exaggerated extensor reflex in reserpinized rats, reportedly specific for 5-HT agonists, can be produced by the hallucinogens of both classes. Moreover, results of stimulus control experiments (Kuhn *et al.*, 1978; Winter, 1978, 1979) reveal that the discriminative stimulus effects of both classes of hallucinogens generalize to quipazine, a 5-HT agonist, and can be blocked by cinanserin, a putative 5-HT antagonist. Furthermore, destruction of 5-HT nerve terminals with intracerebroventricular administration of 5,7-dihydroxytryptamine potentiates the behaviorally disruptive effects of hallucinogens of both classes (Joseph and Appel, 1977; Appel *et al.*, 1977; Commissaris *et al.*, 1980).

Metergoline (1-methyl-8-carbobenzyloxyaminomethyl-10α-ergoline, fig. 1) is a relatively specific central 5-HT antagonist when administered in doses ranging from 0.5 to 2.0 mg/kg with a 180-min pretreatment (Samanin *et al.*, 1980). Higher doses of this compound competitively antagonize the "5-HT behavioral syndrome" produced by 5-HT agonists and hallucinogens of both classes (Sloviter *et al.*, 1980). Moreover, the results of Fuxe *et al.* (1975) have led these authors to suggest that metergoline may be useful as an antidote against the effects of hallucinogens. The present study was designed to examine the effects of metergoline on the disruption of FR-40 operant behavior produced by four well known hallucinogens: LSD and

Received for publication August 28, 1980.
[1] This work was supported by Grant DA-01836 from the National Institute on Drug Abuse.
[2] A predoctoral student supported by U.S. Public Health Service Training Grant GM07392.
[3] Present address: Department of Psychiatry, Yale University, Connecticut Mental Health Center, 34 Park St., New Haven, CT 06508.
[4] Present address: Department of Pharmacology and Therapeutics, Texas Tech University Health Science Center, Lubbock, TX 79430.

**ABBREVIATIONS:** 5-HT, 5-hydroxytryptamine; FR-40, fixed-ratio 40; LSD, *d*-lysergic acid diethylamide; DMT, N,N-dimethyltryptamine; DOM, 2,5-dimethoxy-4-methylamphetamine.

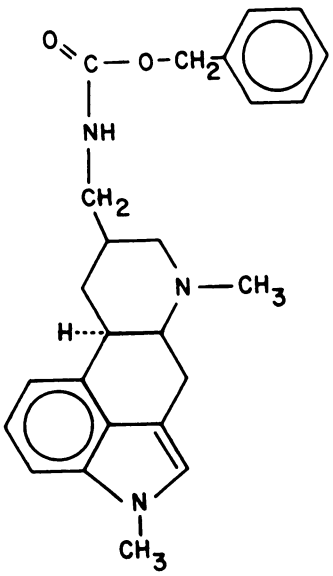

Fig. 1. The structure of metergoline (1-methyl-8-carbobenzyloxyaminomethyl-10-α-ergoline).

DMT as examples of indolealkylamines and DOM and mescaline as examples of phenethylamines.

## Materials and Methods

**Subjects.** Sixteen male Sprague-Dawley rats (Spartan Research Animals, Inc., Haslett, MI) weighing 200 to 250 g at the start of the experiment were used. All animals were housed individually in a room with a 12-hr day-night light cycle (lights on 7:00 A.M.–7:00 P.M.) All subjects had no previous drug treatment before the start of the experiment.

**Behavioral apparatus.** Behavioral training and testing was conducted in one of four standard operant chambers (LVE 143-20-215) equipped with food pellet dispensers; these chambers were located in sound-attenuating boxes. Each chamber contained a single lever which required a force of 10 to 15 g to activate. All experimental events were controlled by electromechanical programming circuits and responses were recorded on electromagnetic counters and cumulative recorders.

Hallucinogens have been reported to produce a pattern of disrupted FR-40 operant responding characterized by periods of nonresponding (Appel and Freedman, 1968; Rech *et al.*, 1975; Commissaris *et al.*, 1980, 1981). To quantitate this pausing, a 10-sec pause interval timer (Commissaris *et al.*, 1980, 1881) was incorporated into the FR-40 program. Each response by the subject reset a 10-sec timer. If the subject responded before 10 sec elapsed, the timer reset and the program continued. If the subject failed to respond during this 10-sec interval, a count was registered and the timer automatically reset. Therefore, the number of counts registered by the pause interval timer was an index of the period of nonresponding in terms of cumulated 10-sec pause intervals. In addition to pause intervals, the number of reinforcements obtained in each FR-40 session was recorded as a reflection of the average response rate. The combined display of the frequency of pause intervals obtained and reinforcements received has been used to differentiate the "pausing" produced by hallucinogens from the slowed and erratic intrasession response rates produced by the stimulant *d*-amphetamine (Commissaris *et al.*, 1980) and the depressant phenobarbital (Commissaris *et al.*, 1981).

**Behavioral procedure.** The subjects (maintained at 75% of their free-feeding weights) were trained to respond on a continuous reinforcement schedule for food (45-mg Noyes pellets). Daily sessions were 40 min in duration. Each animal was run at the same time of day and in the same cage 7 days a week. After all subjects were responding on the continuous reinforcement schedule (1–3 days), a FR schedule was introduced and gradually increased to FR-40. Control FR-40 sessions were continued for 2 to 3 weeks, by which time responding was stable for all subjects. At this time, drug testing was conducted. One-half of the subjects received various doses of LSD (12.5–400 μg/kg), mescaline (5.0–28.4 mg/kg) and *d*-amphetamine (0.25–2.0 mg/kg) alone and after pretreatment with metergoline (1.0 mg/kg; 180 min before testing). The other half of the subjects received various doses of DOM (0.125–4.0 mg/kg); DMT (1.0–8.0 mg/kg) and phenobarbital (12.5–50.0 mg/kg) alone and after metergoline pretreatment. All subjects received metergoline alone at some point in the study. The order of drugs and doses administered was completely randomized for each subject. The hallucinogens and *d*-amphetamine were administered immediately before the start of the FR-40 session; phenobarbital was administered 30 min before the start of the session. In these studies, all test days were preceded by at least 3 nondrug days to avoid the possibility of tolerance development.

**Statistical analyses.** Drug effects were assessed by comparing the data from test days to the average of the 3 days before the test day (base line). Student's *t* test for paired data was used to evaluate the effects of individual doses of the hallucinogens. Dose-response relationships with and without metergoline pretreatment were examined by analysis of variance in a block design. In all statistical evaluations, $P < .05$ was used as the criterion for statistical significance.

**Drugs.** All drugs were administered i.p. LSD tartrate (12.5–400 μg/kg), DOM hydrochloride (0.125–4 mg/kg), mescaline hydrochloride (5–28.4 mg/kg), *d*-amphetamine sulfate (0.25–2 mg/kg) and phenobarbital sodium (12.5–50 mg/kg) doses refer to the salt. DMT (1–8 mg/kg) and metergoline (1 mg/kg) doses refer to the free base suspended in 0.5% corn starch. The hallucinogens were obtained from National Institute on Drug Abuse; *d*-amphetamine and phenobarbital were purchased from Sigma Chemical Company (St. Louis, MO); metergoline was a gift from Farmitalia Carlo Erba, Milan, Italy.

## Results

Control FR-40 responding is characterized by a rapid, constant rate of responding with a number of brief "minipauses" (1–3 pause intervals each) throughout the session. These minipauses often but not always follow the delivery of a food pellet. The response pattern of an individual animal is depicted in figure 2, panel A, and the characteristics of control responding in all animals are summarized in table 1. Metergoline treatment alone increased the number of reinforcements obtained and reduced the number of pause intervals produced (table 1; fig. 2, panel E).

The pattern and extent of disruption produced by LSD, DOM and *d*-amphetamine alone or after metergoline pretreatment are illustrated in figure 2. LSD alone (200 μg/kg; panel B) produced a pattern of disrupted FR-40 responding characterized by a fairly long period of nonresponding. Metergoline pretreatment greatly reduced, but did not eliminate, the pause-producing effect of this dose of LSD (panel F). DOM alone (2.0 mg/kg; panel C) produced a prolonged period of nonresponding; metergoline pretreatment completely antagonized this effect (panel G). Administration of *d*-amphetamine (1.0 mg/kg; panel D) produced a pattern of disruption characterized by slowed, erratic intrasession response rates without any clear-cut pausing. Metergoline pretreatment did not alter this pattern of disruption produced by *d*-amphetamine (panel H).

Quantification of the effects of metergoline pretreatment on the disruption of FR-40 performance produced by the indolealkylamine hallucinogens LSD and DMT can be seen in figure 3. In control animals, these agents produced dose-dependent increases in the frequency of pause intervals and dose-dependent decreases in reinforcements. These hallucinogen-induced effects were significantly antagonized by metergoline pretreatment, but the antagonism was surmountable as evidenced by

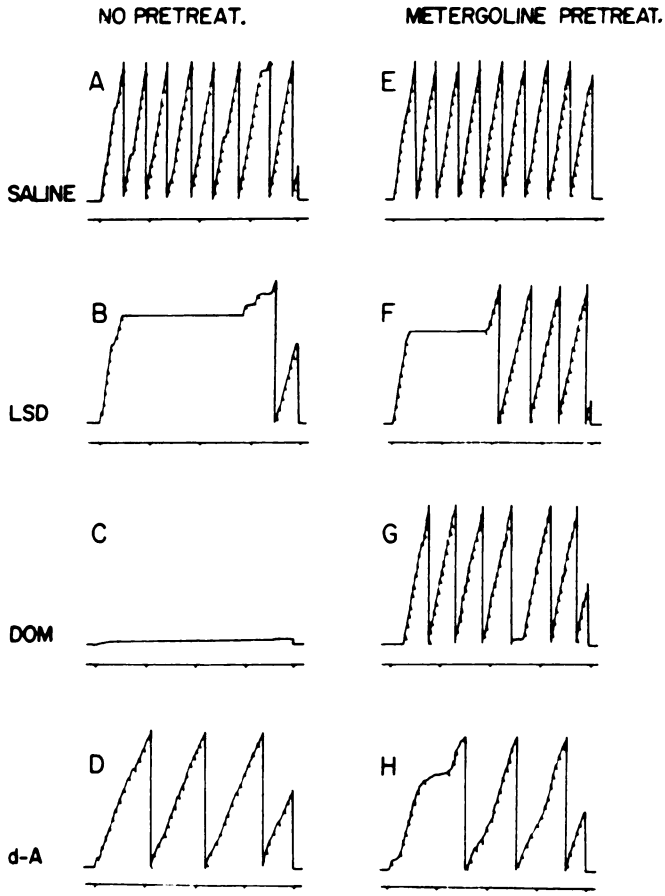


**Fig. 2.** Cumulative recordings illustrating the effects of various treatments on FR-40 responding. A, saline; B, 200 μg/kg of LSD; C, 2.0 mg/kg of DOM; D, 1.0 mg/kg of *d*-amphetamine. Treatments A to D were administered by i.p. injection immediately before the start of the FR-40 session. Treatments E, F, G and H denote metergoline pretreatment (PRETREAT) (1.0 mg/kg, 180 min before the start of the session) and administration of saline, LSD, DOM or *d*-amphetamine, respectively, as in A, B, C and D. Upper trace of each panel: each response produces a slight upward deflection of the pen, 550 upward deflection returns the pen to the start position. Reinforcements are indicated by hashmarks on the record. Lower trace of each panel: the time between vertical hashmarks equals 10 min.

TABLE 1

**The effects of metergoline on characteristics of FR-40 operant responding**

Values represent mean ± S.E.M. for 16 subjects. Metergoline (1 mg/kg) administered i.p. 180 min before the start of the operant session.

| | Pause Intervals | Reinforcements |
|---|---|---|
| Control | 47 ± 4 | 116 ± 7 |
| Metergoline | 29 ± 5* | 126 ± 8* |
| % of control | 63 | 108 |

* $P < .05$; Student's *t*-test for paired values. Reinforcement data normalized by square root transformation to reduce variability before statistical analysis.

the shift to the right in the dose-response curves ($P < .05$ by factorial analysis of variance).

The effects of metergoline pretreatment on the FR-40 disruptive effects of the phenethylamines DOM and mescaline are shown in figure 4. These agents also produced dramatic dose-dependent increases in the frequency of pause intervals and dose-dependent decreases in the number of reinforcements; metergoline pretreatment completely blocked the effects of these agents, even at supramaximal doses (4.0 mg/kg of DOM; 28.4 mg/kg of mescaline).

In control animals, *d*-amphetamine produced a dose-dependent decrease in the number of reinforcements obtained similar to that observed after administration of the hallucinogens, but did not produce an increase in the frequency of pause intervals, except at the highest dose (fig. 5). Examination of the cumulative records from these animals indicated that (as shown in fig. 2, panel D) administration of *d*-amphetamine generally produces slowed, erratic intrasession response rates not characterized by pausing. This pattern of disruption produced by *d*-amphetamine results in a decrease in reinforcements with little or no change in the frequency of pause intervals except at higher doses. Metergoline pretreatment did not significantly alter the effect of *d*-amphetamine on reinforcements or pause intervals.

Phenobarbital, like *d*-amphetamine, produced a dose-dependent decrease in reinforcements without altering the frequency of pause intervals until relatively high doses (35 and 50 mg/kg) were administered (fig. 5). Examination of the cumulative records indicated that, as with *d*-amphetamine, administration of this agent also produced slow and erratic response rates within the FR-40 session. Metergoline pretreatment did not alter the disruptive effects of phenobarbital.

## Discussion

As described previously (Appel and Freedman, 1968; Rech *et al.*, 1975; Commissaris *et al.*, 1980, 1981), the four representative hallucinogenic drugs (LSD, DMT, DOM and mescaline) caused pausing in FR-40 operant behavior. The use of the pause interval counter permitted the clear demonstration that this effect is dose-related for all four agents. The increase in the frequency of pause intervals was well correlated with the decrease in reinforcements induced by these classes of drugs. Phenobarbital and *d*-amphetamine, on the other hand, did not effect a clear dose-related pattern of pausing, even though the decrease in reinforcements was comparable to that observed after the hallucinogens. Thus, although many agents produce dose-dependent decreases in overall response rates, the pause interval timer can be used to differentiate the pausing produced by the hallucinogens from the erratic response rates produced by *d*-amphetamine and phenobarbital. These findings are in agreement with earlier reports from our laboratory comparing *d*-amphetamine and phenobarbital to the hallucinogens LSD, DOM and mescaline (Commissaris *et al.*, 1980, 1981).

Administered alone, metergoline was found to increase reinforcements earned and to reduce the frequency of pause intervals. Since metergoline is purported to be a potent 5-HT receptor antagonist, the results suggest that 5-HT neurons may modulate response rates and promote some pausing in the control FR-40 behavior of rats. This slight degree of pausing may relate to partial satiation within a control session after the subject has earned and consumed a number of reinforcers. Other investigators have described an increase in operant response rates after treatment with 5-HT receptor antagonists (see Graeff, 1974). However, these earlier studies involved responding suppressed by punishment. The present findings indicate that operant schedules devoid of punishment are susceptible to the rate increasing effects of 5-HT antagonists.

Metergoline antagonized the effects of all four hallucinogens investigated. These data support the hypothesis that 5-HT neuronal systems are important in the FR-40 behavioral effects

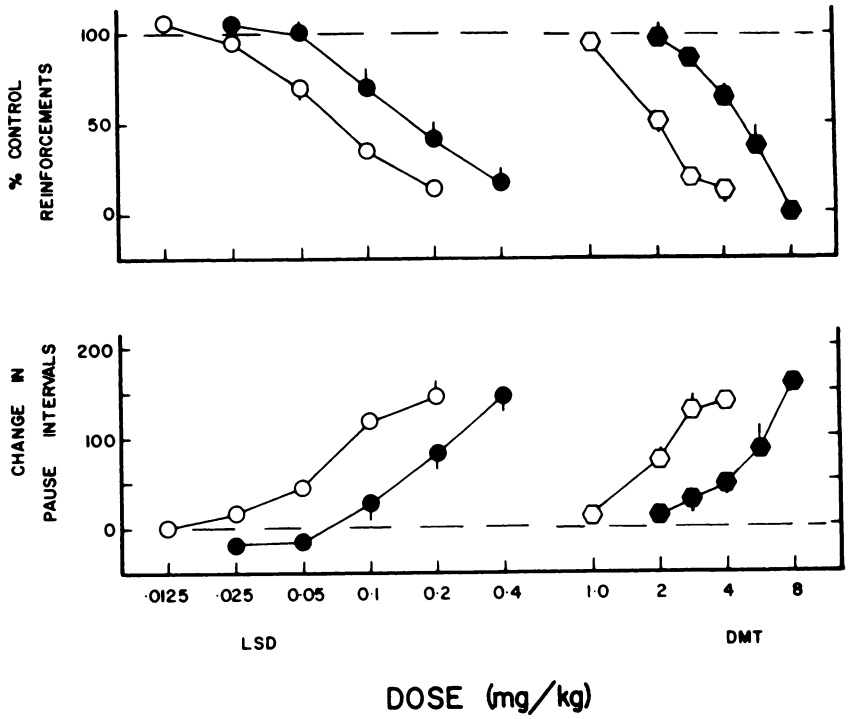


Fig. 3. Metergoline antagonism of the effects of indolealkylamine hallucinogens. The change in pause intervals and percentage of control reinforcements produced by various doses of LSD (circles) and DMT (hexagons) during FR-40 operant sessions are plotted for control (open symbols) or metergoline-pretreated (1 mg/kg, 180 min before session; filled symbols) subjects. Changes in the number of pause intervals and percentage of control reinforcements were determined by comparing the data on test days to the average of the 3 days before the test day (base line). Each symbol and vertical bar represents the mean ± S.E.M. for eight subjects; where vertical lines are not shown the S.E.M. is less than the radius of the symbol.

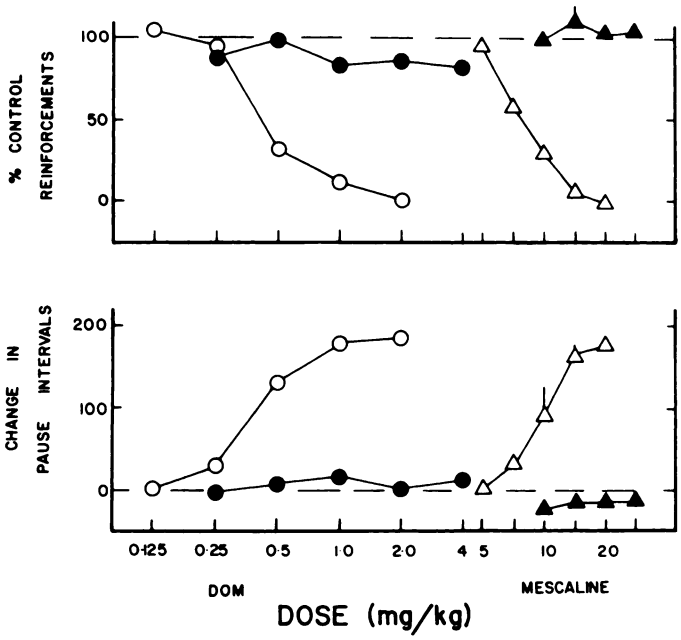


Fig. 4. Metergoline antagonism of the effects of the phenethylamine hallucinogens DOM (circles) and mescaline (triangles). See figure 3 legend for further information.

of the hallucinogens. This finding is in agreement with previous studies involving other types of behavior or neurophysiological responses, which suggested that these hallucinogens are agonists at 5-HT receptors (Andén *et al.*, 1968, 1974; Kuhn *et al.*, 1978; Winter, 1978, 1979; Solviter *et al.*, 1980). Moreover, the fact that metergoline did not attenuate the disruption produced by the nonhallucinogens *d*-amphetamine and phenobarbital suggests that the latter drugs do not produce disruptions of FR-40 operant behavior through interactions with 5-HT neurons.

Sloviter *et al.* (1980) recently have reported that metergoline blocks the capacity of hallucinogens of both classes to produce a 5-HT behavioral syndrome characterized by side-to-side headweaving or head tremor, forepaw treading and splayed hindlimbs. These authors indicated no differences in the metergoline blockade for the phenethylamine *vs.* the indolealkylamine hallucinogens. In the present studies, the antagonism of the effects of DOM and mescaline by metergoline was complete, even for very high doses of the phenethylamines. Additional studies conducted on the antagonism of the phenethylamine DOM have indicated that the metergoline antagonism can be overcome by doses of 8.0 mg/kg of DOM or greater. Moreover, a lower dose of metergoline (0.1 mg/kg) is less effective than the 1.0 mg/kg dose, producing about a 6-fold shift to the right in the DOM dose-response curve (R. L. Commissaris and R. H. Rech, unpublished results). On the other hand, the block of LSD and DMT effects provided by 1.0 mg/kg of metergoline could be overcome by a moderate increase in the doses of these agonists, as the dose-response curves for the effects of these agents were shifted approximately only 2-fold. On the basis of these results alone, it is possible that the metergoline antagonism of the indolealkylamines represents a physiological and not pharmacological antagonism (*i.e.*, summation of pause-increasing and pause decreasing effects). However, in another behavioral paradigm in which metergoline has no effect *per se*, we have found that administration of this agent again produced about a 2-fold shift in the LSD dose-response curve (R. L. Commissaris and R. H. Rech, unpublished results). Furthermore, a physiological antagonism by metergoline would have extended to the disruptive effects of *d*-amphetamine and phenobarbital, which clearly was not the case.

The results of this study strongly implicate 5-HT neurons in the behavioral effects of these two classes of hallucinogens. However, there are now clear-cut differences between the phenethylamine and indolealkylamine classes as shown by their differential antagonism by metergoline. Much of the data may

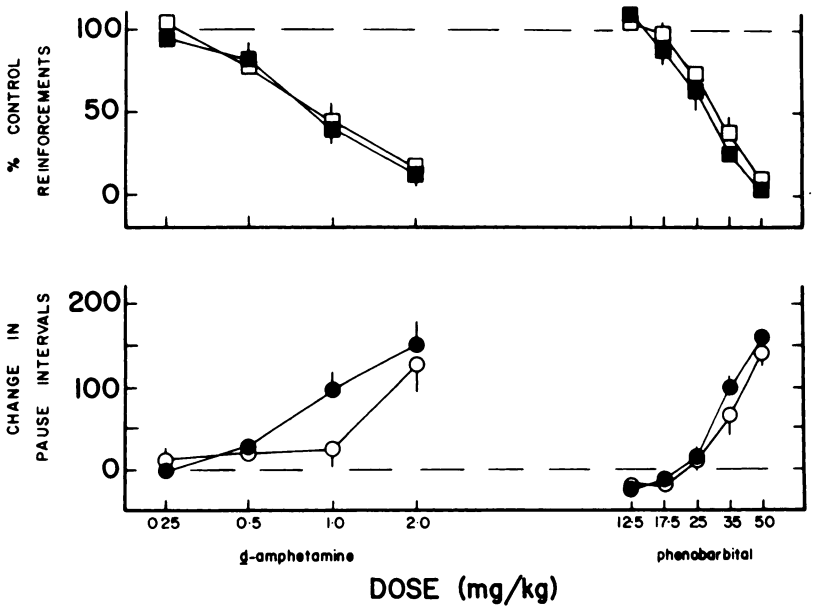


**Fig. 5.** The effects of metergoline on the disruption of FR-40 operant responding produced by *d*-amphetamine and phenobarbital. See figure 3 legend for further information.

be explained by postulating the presence of two or more sites of action for the hallucinogens to affect FR-40 responding. Alternatively, both classes may exert their effects on 5-HT receptors in various regions of the brain, but by different mechanisms. In any case, there is a reasonable theoretical basis for presuming that the two classes of hallucinogens act by different drug-receptor interactions. By using the methods of Schild and others (see Schild, 1957; Barlow, 1964) to estimate absolute antagonist activity and index of activity ($PA_x$) *vs.* an indole or a phenethylamine agonist, one may conclude that the two classes of agonists must involve dissimilar receptor mechanisms. Further analyses of these proposals will require careful, appropriately designed experimental approaches beyond the scope of the present effort.

**Acknowledgments**

The authors acknowledge the excellent technical assistance of Michelle M. Imlay and Charles A. Rewa.

**References**

ANDÉN, N. E., CORRODI, H., FUXE, K. AND HÖKFELT, T.: Evidence for a central 5-hydroxytryptamine receptor stimulation by lysergic acid diethylamide. Br. J. Pharmacol. **34:** 1-7, 1968.

ANDÉN, N. E., CORRODI, H., FUXE, K. AND MEEK, J. L.: Hallucinogenic phenethylamines: Interactions with serotonin turnover and receptors. Eur. J. Pharmacol. *25:* 176-184, 1974.

APPEL, J. B. AND FREEDMAN, D. X.: Tolerance and cross-tolerance among psychotomimetic drugs. Psychopharmacologia **13:** 267-274, 1968.

APPEL, J. B., JOSEPH, J. A., UTSEY, E., HERNANDEZ, L. L. AND BOGGAN, W. O.: Sensitivity to psychoactive drugs and the serotonergic neuronal system. Commun. Psychopharmacol. **1:** 541-551, 1977.

BARLOW, R. B.: Introduction to Chemical Pharmacology, 2nd ed., pp. 42-45, John Wiley and sons, Inc., New York, 1964.

COMMISSARIS, R. L., LYNESS, W. H., CORDON, J. J., MOORE, K. E. AND RECH, R. H.: The effects of *d*-lysergic acid diethylamide (LSD), 2,5-dimethoxy-4-methylamphetamine (DOM) and *d*-amphetamine on operant responding in control and 6-hydroxydopamine-treated rats. Pharmacol. Biochem. Behav. **13:** 621-626, 1980.

COMMISSARIS, R. L., LYNESS, W. H., RECH, R. H. AND MOORE, K. E.: Central 5-hydroxytryptamine and the effects of hallucinogens and phenobarbital on operant responding in rats. Pharmacol. Biochem. Behav., **14:** 595-601, 1981.

FUXE, K., AGNATI, L. AND EVERITT, B.: Effects of methergoline on central monoamine neurons. Evidence for a selective blockade of central 5-HT receptors. Neurosci. Lett. **1:** 283-290, 1975.

GRAEFF, F. G.: Tryptamine antagonists and punished behavior. J. Pharmacol. Exp. Ther. **189:** 344-350, 1974.

JOSEPH, J. A. AND APPEL, J. B.: Behavioral sensitivity to LSD: Dependency upon the pattern of central 5-HT depletion. Pharmacol. Biochem. Behav. **6:** 499-504, 1977.

KUHN, D. M., WHITE, F. J. AND APPEL J. B.: The discriminative stimulus properties of LSD: Mechanisms of action. Neuropharmacology **17:** 257-263, 1978.

RECH, R. H., TILSON, H. A. AND MARQUIS, W. J.: Adaptive changes in behavior after repeated administration of various psychoactive drugs. *In* Advances in Biochemical Psychopharmacology, vol. 13, pp. 263-286, Raven Press, New York, 1975.

SAMANIN, R., BENDOTTI, C., CANDELARESI, G. AND GARATTINI, S.: Specificity of serotonergic involvement in the decrease of food intake induced by quipazine in the rat. Life Sci. **21:** 1259-1266, 1977.

SAMANIN, R., MENNINI, T., FERRARIS, A., BENDOTTI, C. AND BORSINI, F.: Hyper- and hyposensitivity of central serotonin receptors: [$P^3$H]serotonin binding and functional studies in the rat. Brain Res. **189:** 449-457, 1980.

SCHILD, H. O.: Drug antagonism and $PA_x$. Pharmacol. Rev. **9:** 242-246, 1957.

SLOVITER, R., DRUST, E., DAMIANO, B. AND CONNOR, J.: A common mechanism for lysergic acid, indolealkylamine and phenethylamine hallucinogens: Serotonergic mediation of behavioral effects in rats. J. Pharmacol. Exp. Ther. **214:** 231-238, 1980.

WINTER, J. C.: Stimulus properties of phenethylamine hallucinogens and LSD: The role of 5-hydroxytryptamine. J. Pharmacol. Exp. Ther. **204:** 416-423, 1978.

WINTER, J. C.: Quipazine-induced stimulus control in the rat. Psychopharmacology **60:** 265-269, 1979.

**Send reprint requests to:** Dr. Richard H. Rech, Department of Pharmacology and Toxicology, Michigan State University, East Lansing, MI 48824.