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Neurotransmitter Basis of the Behavioral Effects of Hallucinogens[1,2]

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RECH, R. H. AND R. L. COMMISSARIS. *Neurotransmitter basis of the behavioral effects of hallucinogens.* NEUROSCI. BIOBEHAV. REV. 6(4) 521–527, 1982.—Indole and phenethylamine-type hallucinogenic drugs were studied in an FR-40 operant behavioral procedure programmed to quantify "pausing," a behavioral disruption somewhat specific to hallucinatory drug effects. LSD, DOM, DMT and mescaline showed a potency ratio to produce pausing that is well correlated with the hallucinatory potencies of these agents in man. Furthermore, combinations of the hallucinogens interact with potentiation to cause FR-40 pausing, whereas a variety of non-hallucinogenic psychoactive drugs failed to shift the dose-response patterns of pausing for DOM or LSD. Depletion of brain catecholamines by pretreatment with intraventricular 6-OHDA reduced baseline FR-40 rates and attenuated the disruptive effects of *d*-amphetamine, but failed to modify the dose-response patterns of indole and phenethylamine hallucinogens. On the other hand, pretreatment with intraventricular 5,7-DHT to deplete brain 5-HT potentiated the pause-producing effects of the hallucinogens, although the disruptive effects of phenobarbital were not altered by this pretreatment. Injection of 5,7-DHT into the medial forebrain bundle at the hypothalamic level slightly potentiated LSD, attenuated DOM, and did not affect the pausing produced by mescaline. Metergoline pretreatment shifted the LSD and DMT dose-response curves for pausing to the right by a factor of 2–3, but shifted the DOM and mescaline dose-response patterns to a much greater extent. Metergoline alone slightly increased FR-40 response rates and decreased pausing from baseline levels. The patterns of impaired FR-40 performance induced by *d*-amphetamine and phenobarbital were unaltered by pretreatment with metergoline. The indole and phenethylamine classes of hallucinogens appear to disrupt this behavior by an agonistic effect at central 5-HT receptors. However, the two classes of drugs may interact with brain 5-HT systems by somewhat different mechanisms.

Neurotransmitters Hallucinogens Operant behavior Pausing

BOTH indole and phenethylamine classes of hallucinogens, although differing chemically, appear to act as agonists (direct or indirect) at central (5-HT) receptors [2, 11, 13]. We have explored these relationships with a pharmacological approach using a modification of the animal behavioral model employed by Freedman *et al.* [10] and Sparber and Tilson [14,15]. The above-named classes of hallucinogens were found by these investigators to greatly increase periods of non-responding ("pausing") in a fixed-ratio operant schedule of reinforcement. Sparber and Tilson were the first to utilize the intensity of this behavioral disruption to estimate dose-response characteristics of the hallucinogens. They also directly correlated operant behavioral effects of these drugs with neurochemical influences on brain neurotransmitter systems (see below). We have been able to distinguish between drug effects on the FR-40 (fixed-ratio-40) that influence overall responding by an increase in "pausing" (non-responding) as opposed to a drug action that decreases the rate of responding without markedly increasing the inter-response periods. This was accomplished by incorporating a pause-interval counter into the programming, which quantifies 10-sec pauses during the 40-min session. The importance of quantifying the extent of pausing vs decreased rate of responding relates to the analysis of both the magnitude and specificity of hallucinogenic drug action. The experiments described below utilized the FR-40 operant behavioral model with rats and a number of pharmacological manipulations of central catecholamine and 5-HT systems to examine the neurotransmitter implications of the behavioral effects of indole and phenethylamine hallucinogens.

A comparison of the effects of *d*-amphetamine (*d*-A) and lysergic acid diethylamide (LSD) on FR-40 responding (cumulative records) is shown in Fig. 1. Typically *d*-A reduces session responding by a decrease mainly in rate, without a large increase in the number of 10-sec pauses until higher doses reduce overall rate to a very low level. By contrast, LSD and related agents cause an abrupt onset and offset of responding with little intervening change in rate. Dose-response plots of LSD and *d*-A effects on percent of reinforcements and change in pause intervals, relative to

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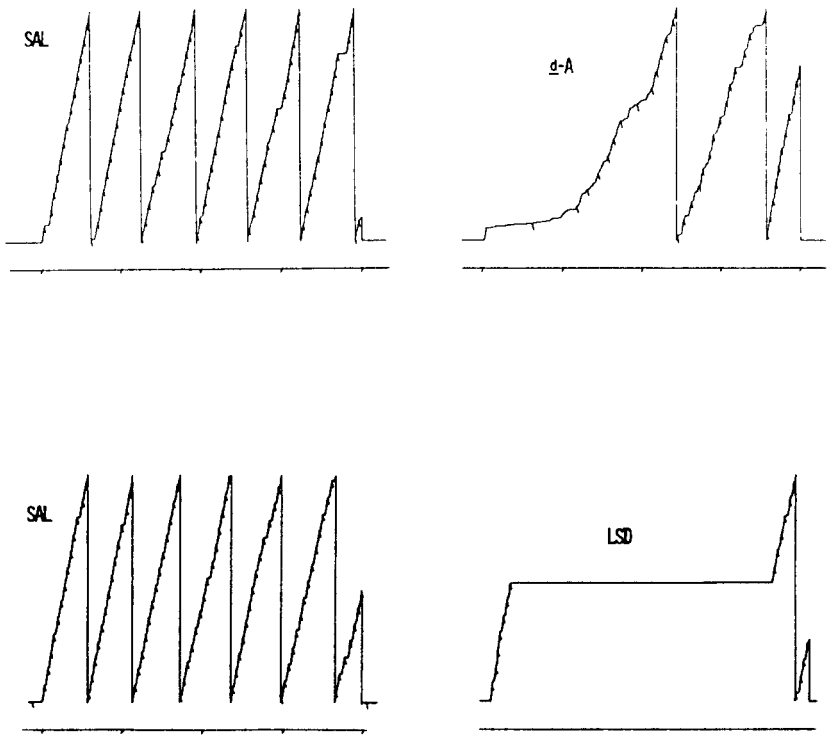

FIG. 1. Cumulative recordings of FR-40 sessions of operant behavior and effects of *d*-amphetamine (*d*-A, 1.0 mg/kg) and lysergic acid diethylamide (LSD, 100 μg/kg). Top trace of each panel: each response slightly deflected the pen upward (full excursion equals approximately 550 responses, after which the pen automatically reset); after each 40 responses delivery of reinforcement was signalled by the oblique ticks. Bottom trace of each panel: ticks mark off 10-min periods. The left-hand panels indicate the effects of saline injections (not different from uninjected controls) in two different subjects. The right-hand panels illustrate the alterations in response pattern by *d*-A (top) and LSD (bottom).

control values, are shown in Fig. 2. There was a proportional change in reinforcements and pause intervals over the entire dose-response curve in the case of LSD. However, the change in pauses after varying doses of *d*-A did not become significant, although *d*-A decreased reinforcements in a dose-related manner.

We compared 4 agents, LSD and dimethyltryptamine (DMT) as indole-type hallucinogens and 2,5-dimethoxy-4-methylamphetamine (DOM) and mescaline (Mesc) as phenethylamine-type representatives, for their dose-response relationships to increase pausing. In Fig. 3, all 4 agents yielded approximately parallel slopes for this effect using a log-dose plot [9]. Additional tests indicated that this effect reached an asymptote at about 175–200 pause intervals for all 4 drugs. The potency ratios for the agents in producing pausing is in good agreement with their ratios to produce hallucinations in man. While not shown in Fig. 3, the decrease in reinforcements by LSD, DOM, DMT and Mesc were proportional and reciprocally related to the increase in pausing over the total dose-response range. That this relationship appears to be at least somewhat specific to the hallucinogenic drugs may be seen in Table 1. LSD, DOM, DMT and Mesc, in doses producing a decrease in reinforcements somewhere near 50%, all produce a significant increase in pause intervals. On the other hand, doses of non-hallucinogenic drugs (*d*-A, phenobarbital, chlorpromazine, cocaine) that reduce reinforcements comparably were not effective in increasing significantly the number of pause intervals in a population of rats. It must be emphasized, however, that individual subjects will on occasion manifest pausing and that larger doses of any psychoactive agent will induce pausing as operant response rates are markedly suppressed.

Further evidence of the commonality of the effects of these hallucinogenic drugs was derived from studying drug combinations [9]. When a subthreshold dose of LSD to cause pausing (20 μg/kg) was combined with a dose range of DOM, the dose-response pattern for DOM to cause pausing was shifted to the left. Similarly, adding a subthreshold dose of mescaline (5 mg/kg) to the dose range of DOM potentiated the pause-producing effects of the latter drug. However, when *d*-A (0.25 mg/kg) was combined with DOM there was no shift in the DOM dose-response curve. *d*-A also failed to shift the LSD dose-response pattern of pausing. Furthermore, other non-hallucinogenic agents (barbiturates, neuroleptics) showed no tendency to shift the DOM dose-response pattern of pausing.

In the next series of experiments we examined the role of

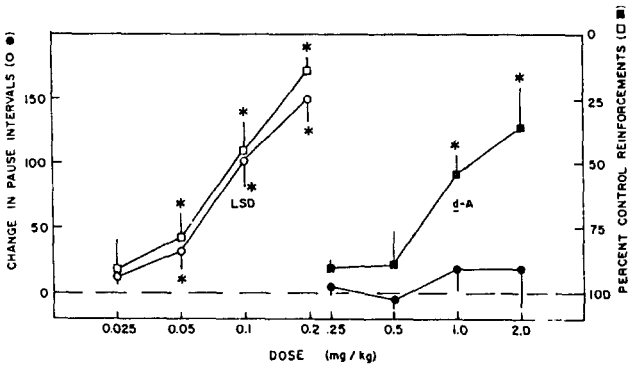

FIG. 2. Dose-response patterns of LSD (left) and *d*-A (right) effects on FR-40 operant responding. The change in pause intervals (circles) and percent reinforcements (squares), relative to control values, are plotted. Each symbol and vertical bar represents the mean±SE for eight subjects. Values marked by an asterisk are significantly different from control ($p<0.05$), by a paired-comparison Student *t*-test.

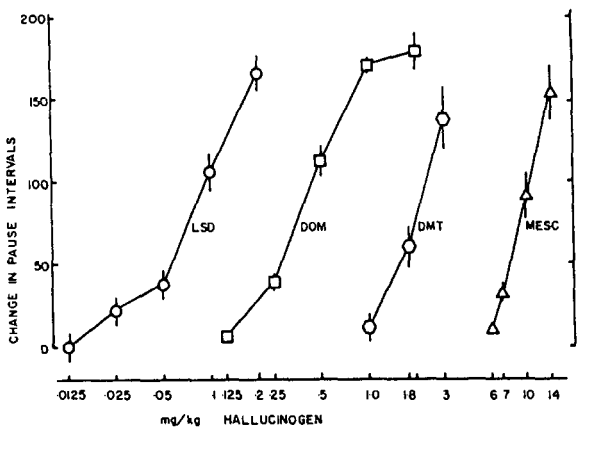

FIG. 3. Dose-response patterns of LSD, 2,5-dimethoxy-4-methylamphetamine (DOM), N,N-dimethyltryptamine (DMT), and mescaline (MESC) for pausing in FR-40 operant behavior (from [9]). Each symbol and vertical bar represent the mean±SE for at least six subjects. Reprinted from [9] with permission; copyright 1981, Pergamon Press, Ltd.

brain catecholamines in the behavioral disruption by hallucinogens by pretreating rats with intracerebroventricular 6-hydroxydopamine (6-OHDA; see [3]). This pretreatment depleted forebrain dopamine and norepinephrine levels to less than 25% of control values, while not significantly altering 5-HT levels in various forebrain regions. The effects of the 6-OHDA pretreatment on the dose-response patterns of LSD, DOM and *d*-A to alter reinforcements and pause intervals are illustrated in Fig. 4. The LSD and DOM dose-response patterns were not significantly affected by the neurotoxin pretreatment. However, comparing the dose-response patterns of *d*-A in vehicle- and 6-OHDA-pretreated rats, there is some attenuation of the behaviorally-disrupting effects on reinforcements by pretreatment with 6-OHDA.

The opposite pattern of neurotransmitter depletion was induced by intracerebroventricular administration of 5,7-dihydroxytryptamine (5,7-DHT), after pretreatment with

TABLE 1

RELATIONSHIP BETWEEN CHANGES IN REINFORCEMENTS AND INCREASES IN PAUSING INDUCED BY HALLUCINOGENS AND NON-HALLUCINOGENIC PSYCHOACTIVE DRUGS

Drug and Dose	N	Percent of Control Reinforcements	Increase in Number of Pause Intervals
Hallucinogens			
0.5 mg/kg DOM	8	44 ± 8*	94 ± 13*
100 μg/kg LSD	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

Each value represents the mean±S.E. Percent of control reinforcements and change in pause intervals were determined as described in Method section. See Method section for details of drug treatments. Reproduced in part from [9] with permission; copyright 1981, Pergamon Press, Ltd.

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

desipramine to protect norepinephrine neurons [5]. Table 2 lists the 5-HT, norepinephrine (NE) and dopamine (DA) levels in various forebrain regions in vehicle and 5,7-DHT-treated rats. The 5-HT concentrations of these regions were markedly reduced while the NE and DA contents were not significantly altered. Similarly treated rats that had been trained in the FR-40 operant procedure were tested for effects of LSD, DOM and Mesc [5]. Changes in pausing from the hallucinogens as a result of neurotoxin pretreatment are depicted in Fig. 5. The lesioned subjects showed a shift of the dose-response curves to the left for all three hallucinogens, i.e., a potentiation. Phenobarbital (not illustrated), in a dose-range of 12.5–50 mg/kg, also disrupted FR-40 performance. However, pretreatment with 5,7-DHT did not result in a shift of the phenobarbital dose-response pattern. Thus, the effects of pretreating with intraventricular 5,7-DHT were not generalized to all drug impairments. Possibly LSD, DOM and Mesc were acting as agonists at supersensitive 5-HT receptors, since some weeks intervened between the neurotoxin pretreatment and testing of the hallucinogenic drugs. Alternatively, the loss of large numbers of 5-HT projections to the forebrain may have decreased the reserve of the system in reference to a disruptive influence of the hallucinogenic agents. PCPA (p-chlorophenylalanine) pretreatment also potentiates the actions of LSD, as reported by Appel *et al.* [1], and the effects of DOM, as reported by us [4].

To pursue further the relationships of brain 5-HT systems to the actions of these hallucinogenic drugs, we administered 5,7-DHT into more restricted brain regions. Administration of 3 μg into the medial forebrain bundle, bilaterally (level of the mid-hypothalamus) in desipramine-pretreated rats, depleted 5-HT in several forebrain areas to 48–71 percent of control [7]. Brain catecholamines were not significantly affected. The effects of LSD, DOM and Mesc on FR-40 pauses

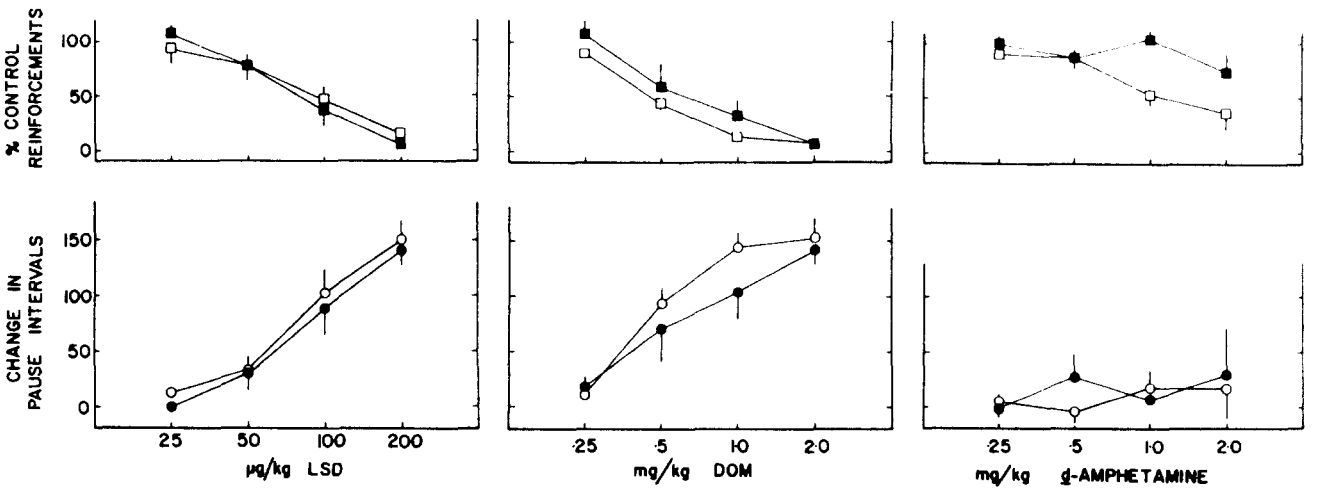

FIG. 4. Dose-response patterns of LSD (left), DOM (middle) and *d*-A (right) to alter reinforcements (squares) and pause intervals (circles) in vehicle (open symbols) or 6-hydroxydopamine-pretested (filled symbols) rats. The neurotoxin (136 μg/10 μl) or vehicle was injected into the lateral cerebral ventricle. Each symbol and vertical bar represent the mean±SE for six or eight subjects. Only the *d*-A effect on reinforcements was significantly attenuated by the pretreatment. Reprinted from [3] with permission; copyright 1980, Ankho International, Inc. Reprinted from [3] with permission; copyright 1980, Ankho International, Inc.

in these subjects, compared to sham-lesioned rats, are shown in Fig. 6. The action of LSD was slightly potentiated for several doses in the mid-range of the dose-response curve. The pausing by DOM was attenuated for several doses at the upper range. However, the dose-response pattern for pausing with Mesc was not altered by the medial forebrain bundle lesion. These results suggest that, while there is some degree of commonality in the way these drugs produce their behavioral effects, there are at least some subtle differences in the discrete mechanisms. The neurotoxin 5,7-DHT was also injected into the nucleus accumbens, septum and amygdala to destroy 5-HT innervation to these brain regions (unpublished results; depletion of septal 5-HT was invariably associated with a decrease in hippocampal 5-HT). In none of these cases did we alter the pattern of the pause-increasing effects of LSD, DOM or Mesc. Therefore, either the 5-HT pathways to these limbic regions appear not to be involved in the behavioral disruption by the indole and phenethylamine hallucinogens or each of these lesions in isolation is insufficient to modify the effects of these drugs.

The last approach was to examine interactions of the indole and phenethylamine hallucinogens with 5-HT antagonists. Some years ago we demonstrated that cinanserin would attenuate the pause effect by a variety of hallucinogens but not the decrease in FR-40 response rate observed after *d*-A or chlorpromazine [12]. In the present study

TABLE 2

EFFECTS OF INTRAVENTRICULAR 5,7-DHT ADMINISTRATION ON THE CONCENTRATIONS OF 5-HT AND NE IN VARIOUS BRAIN REGIONS

	5-HT		NE		DA	
	Vehicle	5,7-DHT	Vehicle	5,7-DHT	Vehicle	5,7-DHT
Cortex	0.34 ± 0.03	0.05 ± 0.02* (16)	0.31 ± 0.01	0.39 ± 0.05 (125)	N.D.	N.D.
Hippocampus	0.28 ± 0.02	0.04 ± 0.01* (15)	0.36 ± 0.02	0.36 ± 0.03 (99)	N.D.	N.D.
Hypothalamus	0.84 ± 0.04	0.28 ± 0.06* (34)	1.80 ± 0.08	1.75 ± 0.19 (97)	N.D.	N.D.
Striatum	0.41 ± 0.03	0.05 ± 0.02* (13)	N.D.	N.D.	13.27 ± 0.32	12.64 ± 0.90 (95)

Data (from [5]) are expressed as μg/g wet tissue weight as determined fluorimetrically. Each value represents the mean±S.E. obtained from four 5,7-DHT-treated (180 μg/10 μl) or six vehicle-treated animals. Numbers in parentheses represent concentration of amine in 5,7-DHT-treated rats expressed as a percentage of vehicle-treated controls. Reproduced in part from [5] with permission; copyright 1981, Ankho International, Inc.

N.D.—amine concentration not determined.

*$p<0.05$ Student's *t*-test.

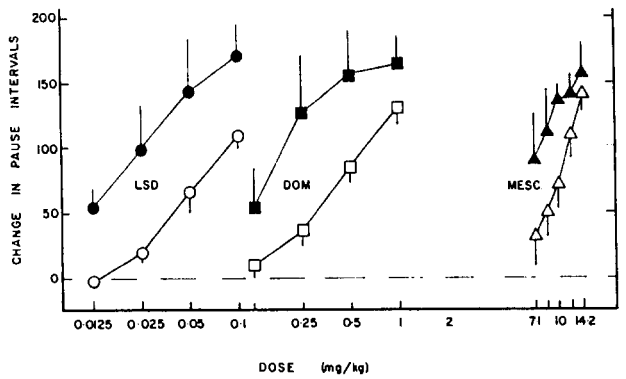

FIG. 5. Dose-response patterns of LSD, DOM and mescaline (MESC) for FR-40 pausing in vehicle- or 5,7-dihydroxytryptamine (5,7-DHT)-pretreated rats (from [5]). Vehicle pretreatment is represented by the open symbols, while the filled symbols represent plots from 5,7-DHT-pretreated subjects. Each point and vertical bar represent the mean±SE for four (5,7-DHT) or six (vehicle) subjects. A significant shift to the left in dose-response curves for all three hallucinogens resulted from the 5,7-DHT pretreatment, $p<0.05$ by factorial analysis of variance. Vehicle or 5,7-DHT creatinine sulfate (180 μg/10 μg) was injected into the lateral cerebral vehicle. Reprinted from [5] with permission; copyright 1981, Ankho International, Inc.

TABLE 3

EFFECTS OF METERGOLINE ON FR-40 OPERANT RESPONDING

	Reinforcements	Pause Responding
Control	116 ± 7	47 ± 6
0.1 mg/kg Metergoline	129 ± 7*	32 ± 6*
	(111)	(68)
1.0 mg/kg Metergoline	126 ± 7*	29 ± 5*
	(108)	(63)

Values represent mean± S.E. for 8 subjects. Metergoline was administered 180 minutes prior to the start of the operant session. Numbers in parentheses indicate percent of control for the values from treated subjects. Reproduced in part from [6] with permission; copyright 1981, Waverly Press, Inc.

*$p<0.05$, Student's t-test for paired values. Reinforcement data normalized by square root transformation prior to statistical analysis.

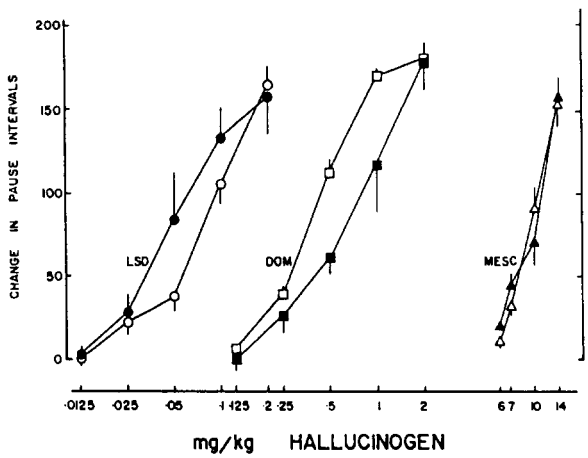

FIG. 6. Dose-response patterns of LSD, DOM and mescaline (MESC) for FR-40 pausing in rats pretreated with vehicle or 5,7-DHT (3 μg, bilaterally) injected into the medial forebrain bundle from [7]. Vehicle pretreatment is represented by the open symbols and 5,7-DHT pretreatment is indicated by the filled symbols. Each point and vertical bar represent the mean±SE for four (5,7-DHT) or eight (vehicle) subjects. The 5,7-DHT pretreatment potentiated the pause effect by LSD, attenuated the pause effect by DOM and did not alter the pattern of mescaline, $p<0.05$ by analysis of variance. Reprinted from [7] with permission; copyright 1981, Ankho International, Inc.

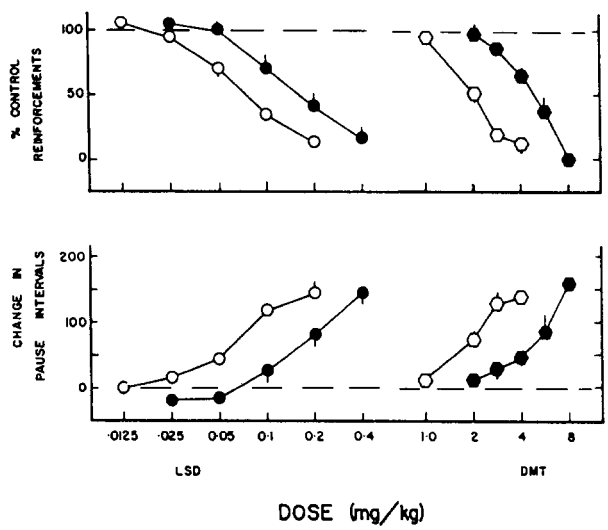

FIG. 7. Antagonism of effects of LSD and DMT (on FR-40 responding) by pretreatment with metergoline (1 mg/kg, 180 min; see [6]). The dose-related decrease in reinforcements and increase in pause intervals are indicated by circles for LSD and hexagons for DMT. Open symbols plot control hallucinogenic drug effects; filled symbols indicate effects after pretreating with metergoline. Each symbol and vertical bar represent the mean±SE for eight subjects (no vertical bar indicates that the SE is less than the radius of the symbol). Metergoline pretreatment significantly shifted the dose-response curves for LSD and DMT to the right. Reprinted from [6] with permission; copyright 1981, Waverly Press, Inc.

we used the more potent 5-HT antagonist metergoline. As indicated in Table 3, doses of 0.1 and 1.0 mg/kg metergoline alone actually cause a significant increase in reinforcements earned and decrease in pause intervals from baseline performance in the FR-40 procedure (see [6]). This effect of metergoline on baseline FR-40 behavior may indicate that the small degree of pausing in control sessions relates to transient satiation for the appetitive drive for food brought about by increased 5-HT activity. Metergoline, by blocking 5-HT receptors, would interfere with this inhibitory modulation. Alternatively, metergoline may be acting in some unspecified manner to somehow enhance discrimination, thereby reducing post-reinforcement pauses and increasing overall response rate. Pretreatment with 1.0 mg/kg metergoline, 180 min prior to the FR-40 session, attenuated the disruptive effects of LSD and DMT, as seen in Fig. 7. Both dose-response patterns for decrease in reinforcements

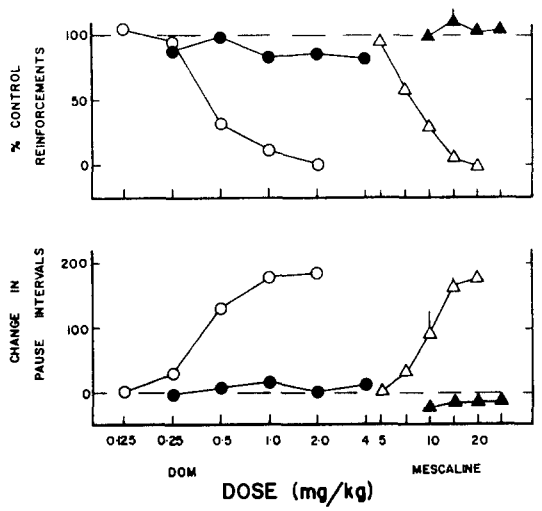

FIG. 8. Antagonism of effects of DOM and mescaline on FR-40 responding by pretreatment with metergoline (1 mg/kg, 180 min; see [6]). The dose-response patterns for decreased reinforcements and increased pausing are indicated by circles for DOM and triangles for mescaline. Open symbols plot control hallucinogenic drug effects; filled symbols plot effects after pretreating with metergoline. Metergoline pretreatment completely antagonized the disruption of behavior over the dose ranges of DOM and mescaline tested in this series of experiments. See Fig. 7 legend for more details. Reprinted from [6] with permission; copyright 1981, Waverly Press, Inc.

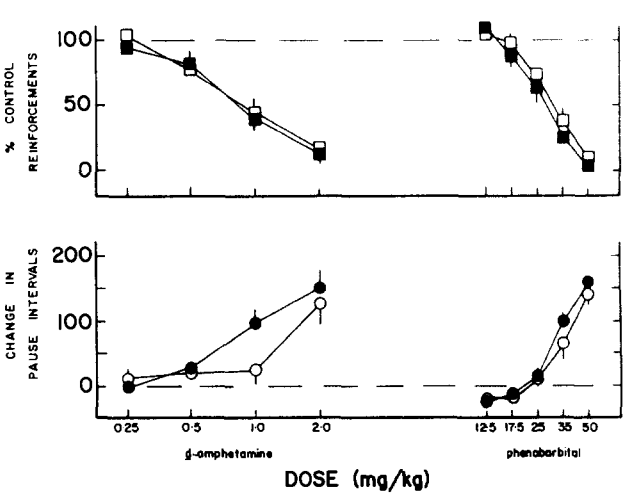

FIG. 9. Effects of metergoline pretreatment on the disruption of FR-40 operant responding by *d*-amphetamine and phenobarbital. The decreased reinforcements and (at the highest doses) inrrease in pausing following *d*-amphetamine or phenobarbital were not significantly altered by pretreating with metergoline. See Fig. 7 for more details. Reprinted from [6] with permission; copyright 1981, Waverly Press, Inc.

and increase in pause intervals by the indole hallucinogens were shifted to the right by a factor of 2–3 times by pretreatment with the antagonist [6]. The influence of 1.0 mg/kg metergoline pretreatment on the FR-40 effects of DOM and Mesc is illustrated in Fig. 8. The antagonist was very effective in blocking the decrease in reinforcements and increase in pause intervals caused by DOM or Mesc, even when the doses of the agonist were increased 2–4 times over that which produced maximal disruption in the absence of metergoline. In subsequent studies of DOM-metergoline interactions we have found the blockade to be surmountable when DOM was increased in dose by a factor of about 16 times ([8]; not illustrated). Thus, there is a prominent difference in the efficacy with which metergoline antagonized the actions of the indole compounds vs the phenethylamine-type drugs. This suggests that the two classes of hallucinogens exert their actions at 5-HT receptors in a different manner. Perhaps the classes bind at different recognition sites on 5-HT receptors, or the phenethylamines may exert their actions by a more indirect mechanism. Evidence for different sites and/or mechanisms of action of LSD and mescaline based on the pattern of release of labeled 5-HT into the CSF and disruption of operant behavior in unrestrained, conscious rats was previously presented by Tilson and Sparber [15,16].

Since metergoline alone tends to increase response rates and decrease pausing from baseline control levels, it may possibly act as a physiological antagonist to the hallucinogenic agents; i.e., the "antagonist" may have opposite effects on behavior that cancel out the actions of LSD, DMT, DOM and Mesc. Therefore, we examined the effects of metergoline pretreatment on the FR-40 disruptive influences of *d*-A and phenobarbital [6], as shown in Fig. 9. Pretreatment with 1.0 mg/kg metergoline 3 hr before the test had no significant effect on the dose-related decrement in reinforcements induced by *d*-A or phenobarbital. Nor were the increases in pausing by the highest doses of *d*-A or phenobarbital reversed. These data indicate that the effects of metergoline are not simply due to a non-specific reactivation of FR-40 responding, since the antagonist was effective in blocking only the behavioral impairments caused by the hallucinogens and not those related to the actions of *d*-A and phenobarbital.

In more recent studies, we have found the 5-HT agonists quipazine and methylchlorophenylpiperazine to distort FR-40 behavior with a dose-related pattern very similar to the hallucinogens [9]. Furthermore, cinanserin or metergoline antagonized the effects of quipazine in a manner very similar to that described for DOM and Mesc. Therefore, the phenethylamine hallucinogens may cause this FR-40 pausing by an action on certain central 5-HT receptors. The indole hallucinogens also may exert a low-dose effect in this same manner. However, LSD and DMT appear to disrupt FR-40 responding in a different manner at somewhat higher doses, and this disruption is insensitive to antagonism by metergoline.

In conclusion, the results of these studies support the concept that both indole and phenethylamine hallucinogens disrupt operant behavior mainly by way of a central tryptaminergic rather than a dopaminergic mechanism. Although both classes of drugs induce very similar patterns of behavioral disruption, there are subtle differences in the ways in which the two classes interact with brain 5-HT systems. Whether these differences represent a different mode of action at the same 5-HT receptors in the central nervous system, the two classes show different selectivities for 5-HT receptors in various brain regions, or the indole representatives exert an additional effect which is not mediated by 5-HT receptors will require a great deal of future research to resolve.

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