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Central 5-Hydroxytryptamine and the Effects of Hallucinogens and Phenobarbital on Operant Responding in Rats

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COMMISSARIS, R. L., W. H. LYNESS, K. E. MOORE AND R. H. RECH. *Central 5-hydroxytryptamine and the effects of hallucinogens and phenobarbital on operant responding in rats.* PHARMAC. BIOCHEM. BEHAV. **14**(5) 595–601, 1981.—The present study was designed to examine the role of 5-hydroxytryptamine (5-HT) neurons in the behavioral effects of *d*-lysergic acid diethylamide (LSD), an indolealkylamine hallucinogen, 2,5-dimethoxy-4-methylamphetamine (DOM) and mescaline, phenethylamine hallucinogens, and phenobarbital, a non-hallucinogen. Male rats, maintained at 70–80% of their free-feeding weights, were trained to press a lever for food pellet reinforcement on a fixed ratio-40 operant schedule. When trained, these rats responded at a constant, rapid rate (approximately 100 responses/min) during daily 40 min test sessions. Administration of hallucinogens caused an abrupt cessation of responding (a "pause"), for some portion of the session. The duration of this pause was dose-dependent for LSD (12.5–100 μg/kg), DOM (0.125–1.0 mg/kg) and mescaline (7.1–14.2 mg/kg). On the other hand, phenobarbital (12.5–50 mg/kg) did not cause pausing, but resulted in slowed, erratic intrasession response rates. When the same tests were repeated in rats that had previously received an intracerebroventricular injection of 5,7-dihydroxytryptamine (5,7-DHT) the dose-response curves for the pausing induced by all three hallucinogens were shifted to the left, while the behavioral disruption produced by phenobarbital was unaltered. In these animals the 5-HT but not the norepinephrine concentrations were markedly reduced in all brain regions examined. These results suggest that 5-HT neurons are involved with the behavioral effects of hallucinogens but not of phenobarbital.

5-Hydroxytryptamine LSD DOM Mescaline Hallucinogens Phenobarbital

BOTH phenethylamine and indolealkylamine hallucinogenic agents appear to exert some of their behavioral effects as a result of 5-hydroxytryptamine (5-HT) agonist properties [3, 4, 14, 17, 24, 25]. On the basis of electrophysiological studies, Aghajanian and co-workers [1, 2, 12] proposed that hallucinogens of both classes inhibit the discharge of 5-HT neurons by activating autoreceptors located on the cell bodies of these neurons in the raphe nuclei. On the other hand, destruction of 5-HT neurons is reported to enhance the behavioral effects of both indolealkylamine (*d*-lysergic acid diethylamide, LSD) and phenethylamine (mescaline-type) hallucinogens [5,13]. In these previous studies, however, only single doses of the hallucinogens were examined. The present study extends these earlier reports by comparing the ability of a full range of doses of LSD, 2,5-dimethoxy-4-methylamphetamine (DOM) and mescaline to disrupt a fixed-ratio (FR-40) operant performance in control rats and in rats pretreated with an intracerebroventricular injection of 5,7-dihydroxytryptamine (5,7-DHT) in order to destroy central 5-HT neurons. The effects in these animals of phenobarbital are also reported. This latter agent, a non-hallucinogenic psychoactive drug, generally disrupts behaviors, including FR-40 performance. However, phenobarbital apparently does not influence behavior through any primary action on central 5-HT neurons and thus represents a control in this attempted correlation with respect to non-specific depressant actions.

METHOD

Animals

Male Sprague-Dawley rats (Spartan Farms, Haslett, MI) weighing 175–200 grams at the start of the experiment were used. All animals were housed individually in a room with a conventional 12-hour day-night light cycle (lights on 0700 to 1900 hr). All subjects were drug-naive prior to the start of the experiment.

Neurochemical Lesioning

All subjects were anesthetized with Equithesin (3 ml/kg) and placed in a stereotaxic apparatus (Kopf). Half of the subjects received intracerebroventricular injections of 5,7-DHT creatinine sulfate (180 μg of the salt/10 μl) and the other half received vehicle (0.1% ascorbate in saline) through a 30 gauge cannula; the coordinates for the injection were

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bregma; 1.5 mm lateral; 3.2 mm below the surface of the brain. All subjects received 40 mg/kg pargyline HCl (Sigma Chemical, St. Louis, MO) and in order to protect against the destruction of norepinephrine neurons 25 mg/kg desipramine HCl (Merrell, Cincinnati, OH) 45 minutes prior to administration of the neurotoxin or vehicle [6]. All subjects were allowed 5–7 days to recover from surgery before behavioral training was begun.

Behavioral Apparatus

Behavioral training and testing was conducted between 800 and 1000 hr in four standard operant chambers (LVE No. 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 10–15 grams to activate. All experimental events were controlled by electromechanical programming circuits and responses were recorded on electromagnetic counters and cumulative recorders. Two parameters were monitored in the operant sessions: (1) the number of reinforcements obtained, a reflection of the average response rate, and (2) the period of non-responding, or "pausing". To quantify the period of non-responding during operant sessions a 10-second pause interval counter [8] was incorporated into the program.

Behavioral Procedure

Following recovery from surgery the animals (maintained at 70–80% of their free-feeding weights) were trained to respond on a continuous reinforcement schedule for food reinforcement (45 mg Noyes pellets). Daily sessions were 40 minutes in duration. Each animal was run at the same time of day and in the same cage seven days a week. After all subjects were responding on the continuous reinforcement schedule (1–3 days), a fixed ratio (FR) schedule was introduced and gradually increased to FR-40. Control FR-40 sessions were continued for 2–3 weeks, by which time responding was stable for all rats. Drug testing was then initiated. Each rat received all doses of LSD (12.5, 25, 50 and 100 μg/kg), DOM (0.125, 0.25, 0.5 and 1.0 mg/kg), mescaline (7.1, 8.5, 12.5 and 14.2 mg/kg), and phenobarbital (12.5, 17.5, 25, 35, and 50 mg/kg); the order of drugs and doses administered was completely randomized for each rat. The hallucinogens were administered immediately before the start of the FR-40 session; phenobarbital was administered thirty minutes prior to the start of the session. All drug test days were preceded by at least three non-drug days to avoid the possibility of tolerance development.

Brain Amine Determinations

Twenty-four hours after the last test dose, the subjects were sacrificed, their brains were removed, and the concentrations of 5-HT and norepinephrine (NE) in selected brain regions (cortex, hippocampus, hypothalamus and striatum) were determined by fluorometric procedures [7,10]. In addition, the concentrations of 5-HT and the dopamine metabolite dihydroxyphenylacetic acid (DOPAC) were determined in the septum using high performance liquid chromatography with electrochemical detection [11,15].

Statistical Analyses

The effects of 5,7-DHT treatment on control FR-40 response parameters and regional brain amine concentrations were compared to vehicle treatment using Student's *t*-test.

TABLE 1

FR-40 OPERANT RESPONSE PARAMETERS IN VEHICLE- OR 5,7-DHT-PRETREATED RATS

Treatment	Reinforcements	Pause Intervals
Vehicle	104 ± 6	70 ± 13
5,7-DHT	81 ± 6	73 ± 19
Percent of vehicle value	77%	105%

Each value represents the mean ± S.E.M. obtained from four 5,7-DHT-treated or six vehicle-treated subjects. Average response parameters for each subject were determined as the mean of the control (no injection) FR-40 sessions throughout the study. No significant differences between vehicle- and 5,7-DHT-treated animals were found.

Drug effects were assessed by comparing the data from test days to the average of the three days prior to the test day (baseline). Student's *t*-test for paired data was used to evaluate the effects of individual doses of the drugs. Dose-response relationships for the drugs were examined by analysis of variance in a block design. In all statistical evaluations $p<0.05$ was used as the criterion for statistical significance.

Drugs

LSD tartrate (N.I.D.A.), DOM hydrochloride (N.I.D.A.), mescaline hydrochloride (N.I.D.A.) and sodium phenobarbital (Sigma Chemical Co.) were administered intraperitoneally; doses refer to the salts.

RESULTS

Control FR-40 responding is characterized by a rapid constant rate of responding throughout the session, with brief pauses usually following the delivery of the food pellet reinforcement. In the present study vehicle-treated subjects received 104±6 reinforcements and produced 70±13 pause intervals in control FR-40 sessions. 5,7-DHT treatment did not significantly alter these characteristics of FR-40 responding (Table 1). Administration of the hallucinogens caused a cessation of FR-40 responding for some portion of the test session ("pausing"), followed by reinstatement of responding at or very near the control response rate. This pattern of disruption resulted in a decrease in reinforcements received and an increase in the number of pause intervals produced. The pausing was not due to motor deficits since these agents did not cause ataxia or a loss of motor function.

On the other hand, phenobarbital most often produced slowed, erratic response rates throughout the session with no clear-cut "pausing". This pattern of disruption resulted in a decrease in reinforcements received, but did not affect the number of pause intervals produced. Higher doses (35, 50 mg/kg) produced "pausing" in some animals, but this pausing was associated with ataxia and motor deficits. Cumulative recordings illustrating the effects of saline, LSD and phenobarbital in vehicle- and 5,7-DHT-treated subjects are shown in Fig. 1.

Table 2 quantitates the effects of the hallucinogens and phenobarbital on FR-40 responding. In vehicle-treated subjects, all four agents produced effects ranging from no

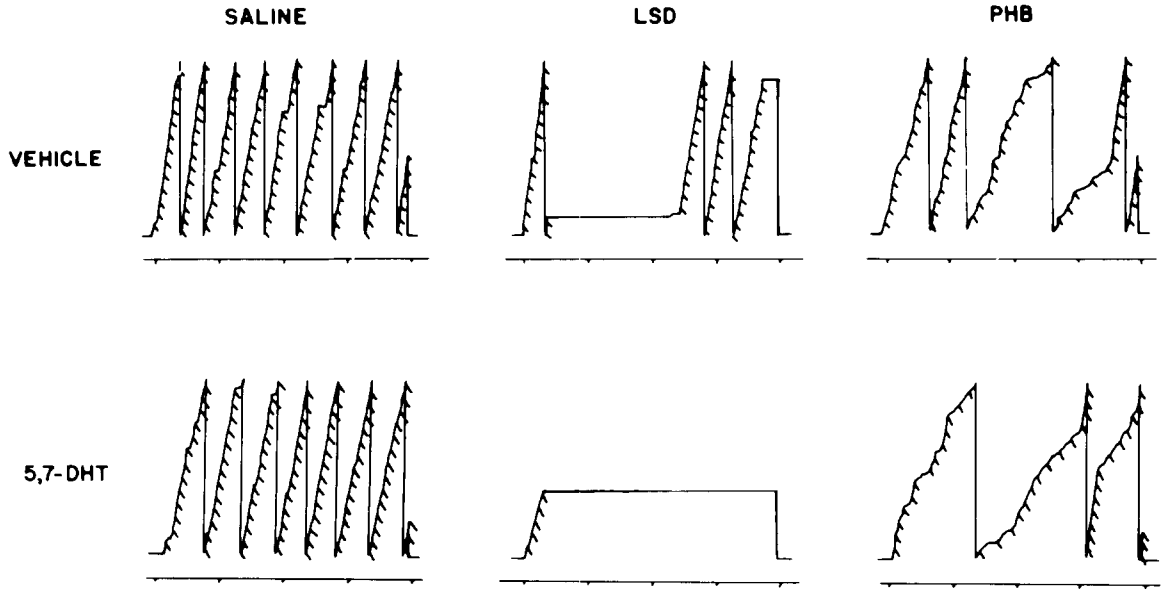

FIG. 1. Cumulative recordings from one vehicle-pretreated subject (top row) and one 5,7-DHT-pretreated subject (bottom row) illustrating the effects of saline, LSD (100 μg/kg) and phenobarbital (PHB; 25 mg/kg) administration on FR-40 responding.

TABLE 2

RELATIONSHIP BETWEEN DECREASE IN REINFORCEMENTS AND INCREASE IN PAUSE INTERVALS IN FR-40 BEHAVIOR OF RATS ADMINISTERED VARIOUS DOSES OF LSD, DOM, MESCALINE AND PHENOBARBITAL

		Vehicle-Treated		5,7-DHT-Treated	
	Dose (mg/kg)	Change In Pause Intervals	Percent of Control Reinforcements	Change In Pause Intervals	Percent of Control Reinforcements
LSD	0.0125	−3.0 ± 3.1	106.0 ± 2.0	55.0 ± 15.3*	70.8 ± 8.9*
	0.0250	19.0 ± 6.5*	90.8 ± 6.9*	98.0 ± 30.0*	40.5 ± 11.7*
	0.0500	66.8 ± 15.6*	54.4 ± 10.7*	143.5 ± 39.3*	22.3 ± 13.8*
	0.1000	109.0 ± 9.4*	33.6 ± 7.7*	171.5 ± 24.3*	2.5 ± 1.9*
DOM	0.125	10.2 ± 7.7	89.9 ± 5.9	54.3 ± 30.0	77.8 ± 14.2
	0.250	36.7 ± 10.1*	80.7 ± 2.8*	126.8 ± 45.2*	27.5 ± 13.4*
	0.500	85.2 ± 9.3*	44.3 ± 5.0*	156.0 ± 33.5*	10.8 ± 4.4*
	1.000	131.7 ± 11.6*	18.8 ± 3.3*	104.5 ± 21.2*	7.8 ± 3.6*
Mescaline	7.1	31.8 ± 23.9	63.0 ± 59.3	90.0 ± 37.2*	43.0 ± 15.5*
	8.5	50.0 ± 17.8*	59.3 ± 21.3*	111.3 ± 35.5*	26.3 ± 18.9*
	10.0	71.5 ± 18.8*	51.5 ± 15.2*	136.3 ± 13.1*	14.5 ± 2.6*
	12.5	109.5 ± 17.5*	29.3 ± 9.3*	141.3 ± 16.0*	11.0 ± 4.1*
	14.2	141.5 ± 13.5*	10.8 ± 5.2*	156.0 ± 26.5*	4.8 ± 3.3*
Phenobarbital	12.5	−17.6 ± 9.3	103.0 ± 5.0	−5.3 ± 8.1	104.8 ± 19.7
	17.5	32.0 ± 20.8	65.8 ± 14.6*	12.3 ± 15.6	80.8 ± 17.3
	25.0	5.6 ± 14.8	67.4 ± 9.6*	−11.0 ± 9.3	76.5 ± 22.9*
	35.0	64.7 ± 18.0*	28.7 ± 8.4*	48.3 ± 31.6	49.3 ± 22.9*
	50.0	59.2 ± 23.5*	18.7 ± 6.1*	130.3 ± 22.7*	1.0 ± 0.6*

Values represent mean ± S.E.M. as determined from 6 vehicle- and 4 5,7-DHT-treated subjects. Change in pause intervals and percent of control reinforcements was determined by comparing the results on test days to the average of the three days prior to the test day (baseline).

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

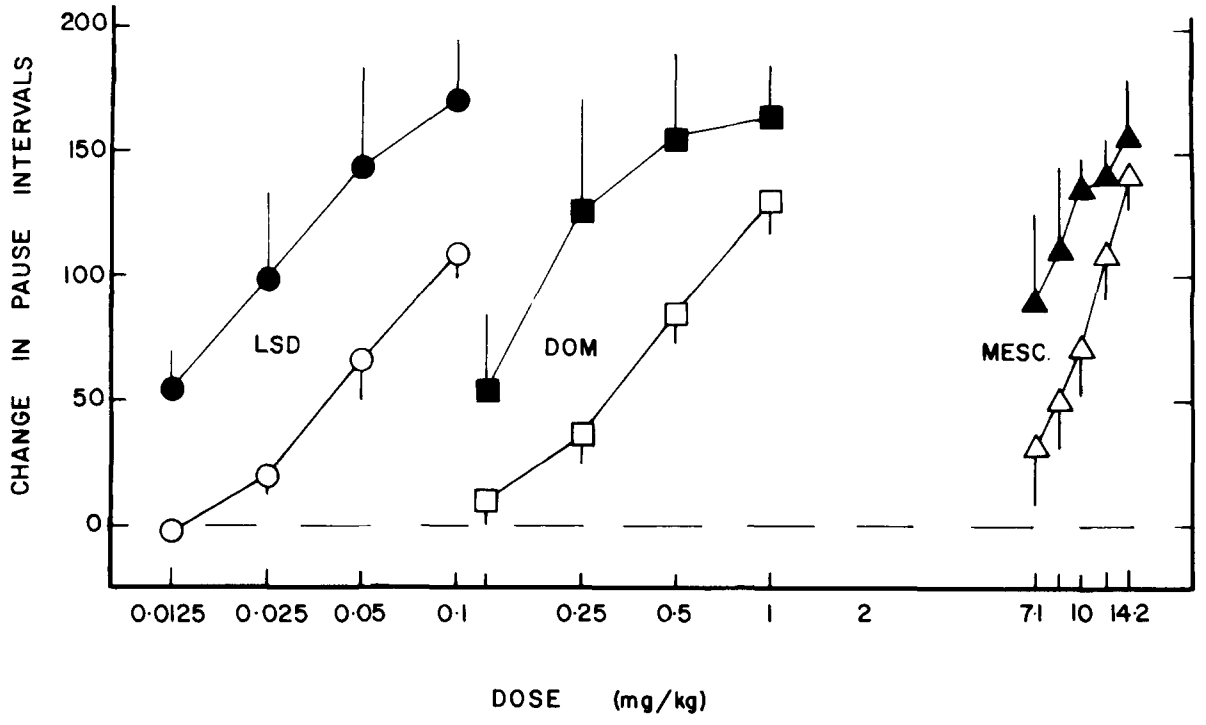

FIG. 2. The effects of LSD, DOM and mescaline on FR-40 operant responding in vehicle- or 5,7-DHT-treated rats. The change in pause intervals produced by various doses of LSD (circles), DOM (squares) and mescaline (triangles), during FR-40 operant sessions in vehicle- (open symbols) or 5,7-DHT-pretreated (filled symbols) subjects is shown. Change in pause intervals was determined by comparing the results on the drug test days to the average of the three days prior to the test day (baseline). See Table 1 for control FR-40 response parameters. Each symbol and vertical bar represents the mean ± SEM for four (5,7-DHT) or six (vehicle) subjects. Potentiation of the effects of all three agents after 5,7-DHT is indicated by the significant shifts to the left in the dose-response curves, $p<0.05$ by factorial analysis of variance.

change in reinforcements received at the lowest doses to nearly complete disruption of FR-40 behavior at the highest doses. The hallucinogens also produced a concomitant increase in pause intervals which was well correlated with the decrease in reinforcements received. This increase in pause intervals was between 70–100 over baseline values following doses of the hallucinogens which decreased reinforcements by nearly 50 percent (50 μg/kg LSD, 0.5 mg/kg DOM and 10.0 mg/kg mescaline). In contrast, the 25.0 mg/kg dose of phenobarbital, which decreased the number of reinforcements received to less than 70 percent of control, had no effect on the number of pause intervals produced. Moreover, the 50.0 mg/kg dose of this latter agent, while decreasing reinforcements to less than 20 percent of control, still produced a mean increase of less than 60 pause intervals.

In the 5,7-DHT treated subjects, the effects of the hallucinogens on both reinforcements received and pause intervals produced were potentiated (Table 2; Fig. 2). Moreover, these two measures were still well correlated for the hallucinogens in the 5,7-DHT-treated subjects. The effects of phenobarbital were not altered by 5,7-DHT treatment (Table 2, Fig. 3). In the 5,7-DHT-treated subjects, as with the vehicle-treated subjects, there was a dissociation between the phenobarbital-induced decrease in reinforcements received and the change in pause intervals produced. For example, 25.0 mg/kg phenobarbital decreased reinforcements received by almost 25 percent but actually produced a tendency to *decrease*, not increase, the number of pause intervals.

Treatment with 5,7-DHT significantly decreased 5-HT concentrations in the cortex, hippocampus, hypothalamus and striatum, while NE concentrations in those regions examined were unaltered relative to vehicle-treated controls (Table 3). Concentrations of 5-HT in the septum of 5,7-DHT-treated subjects were not significantly different from blank measurements at the level of sensitivity of the HPLC method (<3 ng/mg protein). These values were significantly different from vehicle-treated values of 54±3 ng/mg protein ($p<0.05$, 95% confidence limits). Septal DOPAC concentrations in the 5,7-DHT treated subjects, 4.0±0.9 ng/mg protein, were not significantly different from vehicle treated subjects, 4.3±0.4 ng/mg protein.

DISCUSSION

As reported previously hallucinogens produce a disruption of FR-40 behavior which is characterized by periods of non-responding [8, 9, 17]. This dose-related effect was dramatically potentiated by 5,7-DHT pretreatment to about the same extent for LSD, DOM and mescaline. The effects of phenobarbital were considerably different, however. In vehicle-treated animals this agent produced a disruption of behavior characterized by periods of erratic responding, a

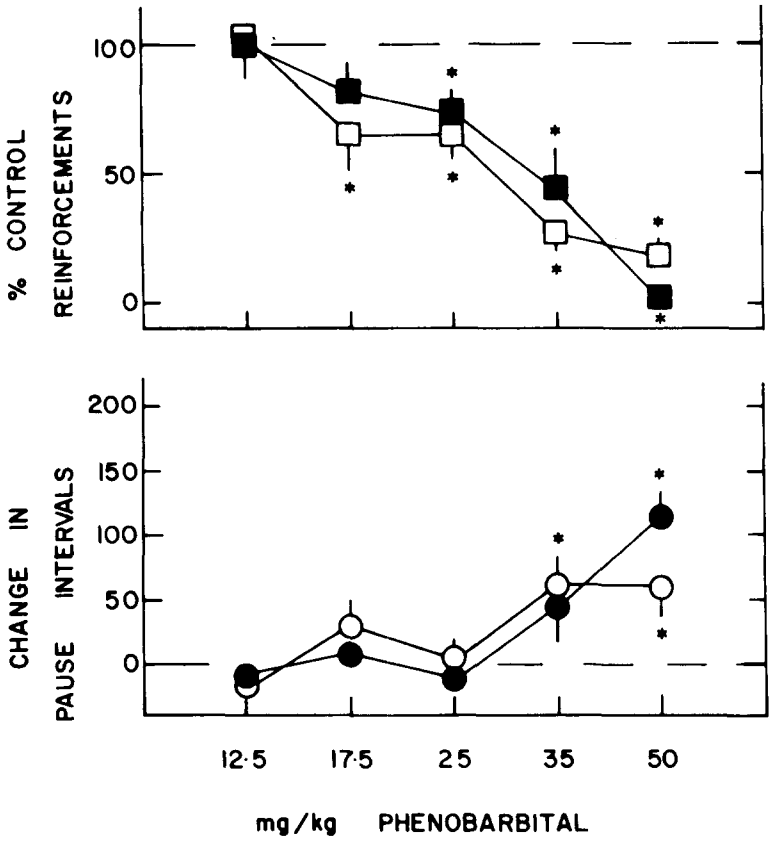

FIG. 3. The effects of phenobarbital on FR-40 operant responding in vehicle- and 5,7-DHT-treated rats. The change in pause intervals (bottom panel) and percent of control reinforcements obtained (top panel) produced by various doses of phenobarbital in vehicle- (open squares) or 5,7-DHT-treated (filled squares) subjects. Change in pause intervals and percent of control reinforcements determined by comparing results on test days to baseline. See Fig. 1 legend for further information. *Significantly different from baseline values; $p<0.05$, Student's t-test for paired values. There was no significant difference between the dose-response curves in vehicle- and 5,7-DHT-treated rats.

TABLE 3

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

	5-HT		NE	
	Vehicle	5,7-DHT	Vehicle	5,7-DHT
Cortex	340 ± 29	53 ± 18* (16)	311 ± 12	389 ± 47 (125)
Hippocampus	279 ± 15	42 ± 8* (15)	364 ± 21	361 ± 32 (99)
Hypothalamus	836 ± 40	282 ± 61* (34)	1796 ± 79	1751 ± 189 (97)
Striatum	408 ± 27	53 ± 18* (13)	n.d.	n.d.

Data are expressed as ng/g wet tissue weight as determined fluorometrically. Each value represents the mean ± S.E.M. 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 expressed as a percentage of vehicle-treated controls.

n.d.=amine concentration not determined.

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

finding which is consistent with previous experience in our laboratory [9]. This pattern of disruption produced by phenobarbital resulted in a decrease in reinforcements obtained similar to that observed with the hallucinogens, but without "pausing", as quantified by the use of the pause interval measurement. This lack of relationship between the decrease in reinforcements and increase in pause intervals has been observed in previous studies involving the CNS stimulant *d*-amphetamine [8]. Destruction of 5-HT neurons by 5,7-DHT treatment did not alter the effects of phenobarbital.

These data indicate that central 5-HT systems are important in the disruptive effects of the hallucinogens LSD, DOM and mescaline. Moreover, these effects seem to be somewhat specific, since 5,7-DHT pretreatment failed to alter the disruptive effects of phenobarbital. These findings extend earlier studies by Appel *et al.* [5] and Joseph and Appel [13] in which it was reported that 5,7-DHT treatment enhanced the FR disruptive effects of single doses of LSD and mescaline and demonstrate that the entire dose-response pattern of the hallucinogens is displaced to the left by the pretreatment.

The precise mechanism for the potentiation of the effects of the hallucinogens is unknown at this time, but several hypotheses may be considered. One possible explanation is

that, following 5,7-DHT treatment, the hallucinogens are acting as agonists at supersensitive 5-HT receptors. A number of investigators have suggested that hallucinogens are agonists at postsynaptic central 5-HT receptors [3, 4, 14, 24, 25]. The putative 5-HT antagonists methergoline and cinanserin block the decrease in reinforcements and "pause-producing" effects of hallucinogens without attenuating the effects of *d*-amphetamine or phenobarbital [9,17]. Moreover, Nelson *et al.* [16] have reported an increase in the number of 5-HT binding sites (receptor supersensitivity) following 5,7-DHT treatment. Therefore, assuming the hallucinogens are acting as postsynaptic agonists in control animals, it may be postulated that these agonists exhibit a greater effect in 5,7-DHT-pretreated animals because they interact with an increased number of receptors. However, a number of other drugs (e.g., fenfluramine, *p*-chloroamphetamine) are presumed to activate post-synaptic 5-HT receptors [20], but they are not hallucinogenic in man. Perhaps the hallucinogens produce a particular pattern of post-synaptic receptor activation which differs from that produced by fenfluramine and *p*- chloroamphetamine, and this difference accounts for the hallucinogenic effects. Adequate testing of this hypothesis will have to await further experimentation with other 5-HT receptor agonists and antagonists.

Another possible explanation for these data relates to the hypothesis for hallucinogenic drug actions originally proposed by Aghajanian *et al.* [1]. According to this hypothesis, hallucinogens activate autoreceptors on the cell bodies of 5-HT neurons in the raphe nuclei [1,12] which, in turn, results in a cessation of impulse traffic in these neurons. Since many central 5-HT neurons appear to be tonically inhibitory in nature [2] a reduction in activity of these neurons would result in "disinhibition" in many forebrain areas and presumably in hallucinations as higher centers received excessive and inappropriate input. The threshold for the effects of the hallucinogens would be determined by the concentration of drug required to inhibit raphe cell firing. In 5,7-DHT-treated animals, in which a large portion of the 5-HT pathways to the forebrain have been destroyed, this threshold would be lowered, relative to control subjects, and the effects of the hallucinogens would be potentiated as described here. One major problem with the raphe neuron inhibition hypothesis, however, is that a number of non-hallucinogenic agents are also potent inhibitors of raphe cell activity. This list includes the LSD analogue lisuride [18], the 5-HT precursor 5-hydroxytryptophan [21] and the 5-HT releasing agents *p*-chloroamphetamine and fenfluramine [19]. Moreover, Trulson and co-workers [22,23] have demonstrated that hallucinogen-induced inhibition of raphe cell activity persists despite the demonstration of tolerance to the behaviorally disruptive effects of these agents in the same animals. These discrepancies indicate that current hypotheses of hallucinogenic drug action are incomplete in explaining mechanisms and/or sites. Although there is sufficient evidence to implicate central 5-HT neurons, the particular imbalance in brain functions related to hallucinogenic drug effects appears not to be adequately described by any of the current theories.

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