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A Common Mechanism for Lysergic Acid, Indolealkylamine and Phenethylamine Hallucinogens: Serotonergic Mediation of Behavioral Effects in Rats[1]

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ABSTRACT

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A rat behavioral model that reflects central serotonin (5-HT) receptor activation *in vivo* was utilized in a study of indole and phenethylamine hallucinogens. Lysergic acid diethylamide (LSD; 1–4 mg/kg i.p.) caused the 5-HT behavioral syndrome (side-to-side headweaving or head tremor, forepaw padding and splayed hindlimbs). Doses of LSD (10 and 100 μg/kg), which alone were too low to cause the syndrome, shifted the dose-response curve for 5-methoxy-N,N-dimethyltryptamine (a 5-HT receptor agonist) to the left. No antagonist effects of LSD were detected at any dose tested (10 μg/kg–4 mg/kg). Bromo-LSD, a nonhallucinogenic congener of LSD that attenuates LSD hallucinations in man, did not cause the 5-HT behavioral syndrome over a wide dose range (1–100 mg/kg). However, bromo-LSD (1–10 mg/kg) did block the behavioral effects of LSD, *i.e.*, shifted the LSD dose-response curve to the right. Bromo-LSD (1–10 mg/kg) also shifted the 5-methoxy-N,N-dimethyltryptamine dose-response curve to the right, as did the presumed 5-HT receptor antagonists methysergide, metergoline and mianserine. All indole and phenethylamine hallucinogens tested (5-methoxy-N,N-dimethyltryptamine, N,N-dimethyltryptamine, N,N-diethyltryptamine, ibogaine, mescaline, *p*-methoxyamphetamine and four other methoxy-substituted amphetamines) evoked the same 5-HT behavioral syndrome in rats as did LSD. Studies on the mechanism by which these compounds activated 5-HT receptors revealed that all except *p*-methoxyamphetamine were direct 5-HT agonists. *p*-Methoxyamphetamine produced its behavioral effect primarily through release of endogenous 5-HT. The findings support the hypothesis that lysergic acid, indolealkylamine and phenethylamine hallucinogens share a common mechanism of action, *i.e.*, central 5-HT receptor activation.

The mechanism of action of hallucinogenic compounds, most notably D-lysergic acid diethylamide (LSD), has long been a subject of investigation. Snyder and Richelson (1968) suggested that the key to hallucinogenic efficacy is in the ring structure of LSD. This hypothesis implies that because of structural similarity, hallucinogens of the lysergic acid, indolealkylamine, and phenethylamine types (*e.g.*, LSD, N,N-dimethyltryptamine and mescaline, respectively) interact with the same central receptor site. The "hallucinogenic" receptor, if one exists, is unidentified, but considerable evidence implicates serotonin (5-HT) receptors in the actions of these drugs (see review by Freedman and Halaris, 1978). If 5-HT receptors do mediate some behavioral effects of hallucinogens, it is unclear whether these effects are caused by receptor stimulation or blockade.

Gaddum (1953) reported that LSD antagonized 5-HT contraction of smooth muscle *in vitro* and suggested that LSD might produce hallucinations by blocking 5-HT receptors in brain. The view that LSD is fundamentally a central 5-HT antagonist received impetus from reports that excitation of brain stem neurons by 5-HT applied microiontophoretically was antagonized by i.v. or iontophoretic LSD (Boakes *et al.*, 1970; Couch, 1970; Bradley and Briggs, 1974). However, the observation that D-2-bromo-LSD (BOL) also blocked 5-HT contractions of smooth muscle *in vitro* (Cerletti and Doepfner, 1958) but was not hallucinogenic (Cerletti and Rothlin, 1955; Jarvik *et al.*, 1955; Schneckloth *et al.*, 1957) argued against 5-HT receptor blockade as the mechanism responsible for the behavioral effects of LSD. Conversely, numerous studies provided evidence that LSD and other hallucinogens are 5-HT receptor agonists. LSD was shown to have agonist, as well as antagonist, actions in smooth muscle preparations (Costa, 1956; Shaw and Woolley, 1956). Results with the hindlimb extensor reflex indicated that LSD, 5-methoxy-N,N-dimethyltryptamine (5-MeODMT), *p*-methoxyamphetamine and 2,5-dimethoxy-4-methyl-amphetamine had 5-hydroxy-L-tryptophan (5-HTP)-like effects (Andén *et al.*, 1968, 1974; Fuxe *et al.*, 1972). Studies

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with shaking behavior ("wet dog" shakes or head shakes in rats; head twitches in mice) showed 5-HTP-like effects of LSD, N,N-dimethyltryptamine, 5-MeODMT, psilocybin, mescaline and other compounds (Corne and Pickering, 1967; Bédard and Pycock, 1977). Also, LSD and other hallucinogens have been reported to mimic the inhibitory effects of microiontophoretically applied 5-HT (Haigler and Aghajanian, 1974a; Bramwell and Gönye, 1976). However, these iontophoretic effects of 5-HT were not blocked by the presumed 5-HT receptor antagonists methysergide, metergoline, methiothepin, cyproheptadine or cinanserin (Haigler and Aghajanian, 1974b). In addition, Aghajanian (1976) reported that BOL failed to block the effects of 5-HT or LSD applied iontophoretically. These negative results seem paradoxical, since BOL reportedly blocks LSD hallucinations (Bertino *et al.*, 1959), and, like LSD, potently displaces [^{3}H]-5-HT and [^{3}H]LSD from binding sites in rat brain homogenates (Bennett and Snyder, 1976).

An obstacle to behavioral studies on effects of hallucinogens on central 5-HT mechanisms has been the lack of an animal model that reflects central 5-HT receptor activation *in vivo* with a high degree of specificity. Previous studies have shown that pharmacological treatments that evoke a behavioral syndrome in the rat (simultaneous display of side-to-side headweaving or head tremor, forepaw padding and splayed hindlimbs) do so by stimulating central 5-HT receptors (Grahame-Smith, 1971a; Jacobs, 1976; Sloviter *et al.*, 1978a). The specificity of the 5-HT behavioral syndrome was the subject of an extensive study published previously (Sloviter *et al.*, 1978a). The results indicated that the syndrome is not mediated by, or dependent on, catecholamines. Therefore, it was concluded that this behavioral syndrome can be used as a model to study the serotonergic properties of drugs regardless of concurrent actions these compounds may also exert on catecholamine mechanisms.

Kuhn and Appel (1975) and Trulson and Jacobs (1976) showed that LSD, in relatively high doses, caused the 5-HT behavioral syndrome in rats. In addition, they reported that this behavior could still be evoked after 5-HT depletion, suggesting that LSD was a direct 5-HT agonist. Our experiments with the 5-HT behavioral syndrome were designed to: 1) reveal agonist *vs.* antagonist properties of LSD throughout a wide dose range; 2) detect effects of BOL, if any, on central 5-HT mechanisms; 3) determine whether the serotonergic effects in rats of LSD and BOL parallel their behavioral effects in man; and 4) investigate whether or not hallucinogens, as a class of drugs, share a common serotonergic mechanism.

Methods

Animal treatment. Male Sprague-Dawley descendent rats (Zivic-Miller, Allison Park, PA, 250–400 g) were used for all experiments. The rats were maintained on a 12 hr light/dark cycle with free access to food (Purina Formulab) and water. On the day of the experiment, rats were brought to the laboratory from the animal quarters, weighed, placed in individual metal cages with 1 to 2 cm of corncob bedding and were allowed to habituate for 30 min. Rats were handled only for injection or sacrifice. Brains were removed from the skull within 2 min of decapitation. Tissues were frozen in dry ice, weighed and stored at −80°C for subsequent monoamine analysis.

Drugs. Compounds injected i.p. were: BOL; LSD; (+)-4-methoxyamphetamine HCl (PMA); (+)-3,4,5-trimethoxyamphetamine HCl (TMA); (+)-2,5-dimethoxy-4-bromoamphetamine HCl (DOB); (+)-2,5-dimethoxy-4-methyl-amphetamine HCl (DOM); (*dl*)-2,5-dimethoxyamphetamine HCl (DMA) (all from National Institute on Drug Abuse); 3,4,5-trimethoxyphenethylamine HCl (mescaline), 3,4-dimethoxyphenethylamine HCl (DMPEA); N,N-dimethyltryptamine (DMT); 5-MeODMT; N,N-diethyltryptamine (DET); ibogaine HCl; DL-*p*-chlorophenylalanine methylester HCl (*p*CPA); 5-HTP; and DL-α-methyl-*p*-tyrosine methylester HCl (α*M*pT) (all from Sigma Chemical Company, St. Louis, MO); methysergide maleate (Sandoz Pharmaceuticals, Hanover, NY); metergoline (Farmitalia Inc. Milan, Italy); desipramine HCl (Lakeside Laboratories, Inc., Milwaukee, WI); mianserine HCl (Organon Inc., West Orange, NJ); and pentobarbital sodium (Beecham Laboratories, Inc., Bristol, TN). The compounds were dissolved in 0.9% w/v sodium chloride (saline) with these exceptions: DMT, DET, 5-MeODMT and ibogaine were dissolved in 1% w/v citric acid in saline; metergoline was suspended in polyethylene glycol 400. Doses of drugs in salt form refer to the weight of the salt. Control rats received the appropriate vehicle(s).

Compounds injected into the left lateral cerebroventricle of conscious rats were 6-hydroxydopamine HBr and 5,7-dihydroxytryptamine creatinine sulfate (5,7-DHT). These neurotoxins (both from Sigma Chemical Company) were dissolved in 1% w/v ascorbic acid in saline; doses refer to weight of base compound. As described previously (Sloviter *et al.*, 1978a), 25 mg/kg of desipramine was injected 50 min before 5,7-DHT to increase the specificity of action of 5,7-DHT. Convulsions were controlled with 15 mg/kg of pentobarbital injected i.p. 3 min after 5,7-DHT.

Monoamine assay. Whole brain concentrations of amines were measured for two reasons: 1) to check the possibility that hallucinogens could cause the 5-HT behavioral syndrome by increasing the concentration of brain 5-HT and 2) to substantiate the efficacy of treatments designed to alter amine concentrations, *e.g.*, *p*CPA. It was not a goal in these experiments to determine the effects of hallucinogens on amine turnover, a subject of many previous studies (see review by Freedman and Halaris, 1978).

Frozen brain tissue was homogenized in 0.4 N $HClO_4$, then assayed for norepinephrine (NE), dopamine (DA) and 5-HT by the method of Shellenberger and Gordon (1971). All drugs used were tested for interference in this assay. DMPEA, DOM, DOB, mescaline, DMA, TMA and PMA interfered with 5-HT-ninhydrin fluorescence readings. Brain tissues from rats treated with these compounds were assayed for 5-HT by a modification derived from the method of Maickel and Miller (1968), as follows: 1) to the heptanol aliquot containing 5-HT (Shellenberger and Gordon, 1971) add 2.0 ml of 0.1% w/v cysteine in 0.1 N HCl (cysteine addition increases 5-HT fluorescence (Korf and Valkenburg-Sikkema, 1969); 2) shake for 5 min and centrifuge for 5 min at 2000 rpm; 3) discard heptanol phase; 4) transfer 0.4 ml of acid phase (avoid heptanol contamination) to tubes; 5) add 1.2 ml of 4% *o*-phthalaldehyde in 10 N HCl; 6) heat tubes in 100°C water bath for 15 min; 7) cool to room temperature; and 8) read fluorescence (360–470 mμ). With the modified assay, brain 5-HT concentrations were measured without interference from any phenethylamine except DMPEA.

The average S.E.s within a single assay were 4% for NE and DA and 5% for 5-HT. Amine recoveries (internal standard/external standard) were in the range of 85 to 90% for all amines in the Shellenberger and Gordon (1971) method. In the *o*-phthalaldehyde modified assay, the recovery of 5-HT was 60 to 70%. Values were corrected for recovery.

Behavioral evaluation. The syndrome caused by 5-HT receptor stimulation was evaluated as described previously (Sloviter *et al.*, 1978a). It was considered present, in all-or-none fashion, if rats exhibited simultaneously forepaw padding, splayed hindlimbs and side-to-side headweaving or head tremor. The terms "serotonin behavioral syndrome" or "syndrome" refer specifically to these behavioral signs. Pilot experiments provided information on the latency and duration of the syndrome and on other drug effects, *e.g.*, different behaviors, convulsions, recovery or death. Rats whose brains were assayed for amine concentrations were sacrificed at times coincident with manifestation of the syndrome. Behavioral responses were judged continuously from 1 min after injection until sacrifice by an observer unaware of the treatment. The syndrome was marked present if the three behavioral signs were present simultaneously at any time during the observation period.

Results

Effects of LSD on behavior and monoamine concentrations. LSD (0.5, 1.0, 2.0 and 4.0 mg/kg) caused the 5-HT behavioral syndrome in zero, two, four and four rats in each group (n = 4), respectively. The latency to onset was 1 to 2 min. Responses had durations of 10 to 45 min, depending on dose. In these experiments, LSD (up to 4 mg/kg) never caused convulsions or death. LSD (1, 2 and 4 mg/kg) had no significant effect ($P > .05$) on whole brain concentrations of NE, DA or 5-HT 20 min after injection, a time coincident with display of the syndrome.

Effects of monoamine depletors. Amine synthesis inhibitors and neurotoxins were used to determine whether the 5-HT behavioral syndrome caused by LSD depends on endogenous amines and/or intact amine systems. Reduction of endogenous catecholamine concentrations by α-methyl-p-tyrosine, a tyrosine hydroxylase inhibitor, or by 6-hydroxydopamine, a catecholamine neurotoxin, did not prevent the 5-HT behavioral syndrome after LSD (4 mg/kg), although both pretreatments caused lethargy. Reduction of brain serotonin by pCPA or 5,7-DHT did not prevent the LSD syndrome or make rats lethargic. Drug doses, regimens and the effects of all four pretreatments on brain amine concentrations are presented in table 1.

Effects of LSD on 5-MeODMT dose-response curves. 5-MeODMT (0.25–3.0 mg/kg), a potent hallucinogen and direct 5-HT agonist (Grahame-Smith, 1971b; Fuxe *et al.*, 1972, Sloviter *et al.*, 1978a), caused the 5-HT behavioral syndrome with a time course similar to that of LSD. If LSD has 5-HT receptor effects at low doses, LSD (10 and 100 μg/kg) should shift the 5-MeODMT dose-response curve. Rats received either saline plus 5-MeODMT or LSD plus 5-MeODMT in single i.p. injections. Figure 1 shows that the net effects of LSD administration (10 and 100 μg/kg) were leftward shifts in the 5-MeODMT curves. These are characteristics of an agonist. The experiment with the lower dose (10 μg/kg) of LSD was repeated in another group of rats with similar results.

Effects of BOL and 5-HT antagonists. BOL (1, 5, 10, 25, 50 and 100 mg/kg) never produced the 5-HT behavioral syndrome. Low doses of BOL caused no overt behavioral signs; higher doses (above 10 mg/kg) caused lethargy, *e.g.*, failure to retract hindlimbs when extended manually. At the highest doses tested (50 and 100 mg/kg), BOL caused gasping, ataxia, convulsions and death within 10 min after injection.

The purpose of the following experiments was to determine if BOL possesses 5-HT antagonist properties. Figure 2 shows that the presumed 5-HT antagonists methysergide, mianserine or metergoline (all 10 mg/kg) shifted the 5-MeODMT dose-response curves to the right in parallel, indicative of competitive inhibition. Figure 3 shows that BOL (1 and 10 mg/kg) also shifted the 5-MeODMT curves to the right. Moreover, figure 4 shows that BOL (10 mg/kg) shifted the LSD dose-response curve to the right. BOL (10 mg/kg) was roughly 4 times more potent in blocking the behavioral effects of 5-MeODMT than it was in blocking the behavioral effects of LSD.

Indole hallucinogen effects on behavior and monoamines. Four indole hallucinogens, 5-MeODMT, DMT, DET and ibogaine, caused the same 5-HT behavioral syndrome as did LSD. Table 2 shows dose-response comparisons for indoles. Syndrome latency was approximately 3 to 5 min for all compounds; the durations were 10 to 60 min depending on dose. With ibogaine, whole-body tremor accompanied the syndrome. None of the compounds altered brain NE or 5-HT concentrations ($P > .05$) significantly. Only ibogaine (40 mg/kg) affected brain DA (increased 39% above control; $P < .001$). This experiment was not repeated in other animals to establish the response as a consistent effect of ibogaine. Haubrich and Wang (1977) reported that DMT (20 mg/kg) decreased brain DA by 42% 5 min after injection. We found that DMT (10, 20 and 40 mg/kg) had no effect ($P > .05$) on brain DA concentrations 5, 10 or 15 min after injection, even though these experiments were repeated twice. It seems unlikely that this disparity is due to the specific tissues analyzed (whole brain *vs.* whole brain less medulla-pons and cerebellum), since either sample should contain most of the dopamine present in the brain. Also included in table 2 for the purpose of comparison are data in Mescaline Units (Shulgin *et al.*, 1969) for hallucinogenic potency in man. Note the general positive correlation between hallucinogenic potency in man and serotonergic potency in rats.

Effect of 5-HT depletion. Rats were pretreated with pCPA, an inhibitor of 5-HT synthesis (Koe and Weissman, 1966), to determine whether endogenous 5-HT is necessary for the behavioral effects of hallucinogens. pCPA (400 mg/kg i.p.), given 3 days before behavioral testing or sacrifice for amine assay, did not prevent the 5-HT behavioral syndromes caused by 5-MeODMT (2 mg/kg), DMT (40 mg/kg), DET (10 mg/kg) or ibogaine (40 mg/kg), indicating direct 5-HT receptor agonist actions. The extent of monoamine changes after pCPA treatment is presented in table 3.

Effects of phenethylamine analogs on behavior and monoamines. Seven phenethylamine analogs were tested for

TABLE 1

Effect of amine depletors on monoamine concentrations in rat brain

There were four rats in each group. pCPA (400 mg/kg i.p.) or vehicle was given 72, 48 and 24 hr before sacrifice. αMpT (250 mg/kg i.p.) or vehicle was given 18 hr before sacrifice. 5,7-DHT (200 μg base) or vehicle was injected into the left lateral cerebroventricle 3 days before sacrifice. 6-Hydroxydopamine (250 μg base) or vehicle was injected into the left lateral cerebroventricle on the 6th and 7th day before sacrifice. Values are means (nanograms per gram of frozen tissue) ± S.E.M. % percentage of vehicle control.

Treatment	NE		DA		5-HT	
	Conc.	%	Conc.	%	Conc.	%
Control	370 ± 15	100	628 ± 26	100	443 ± 22	100
pCPA	264 ± 11***	71	541 ± 11*	86	52 ± 5***	12
Control	352 ± 12	100	582 ± 27	100	348 ± 9	100
5,7-DHT	340 ± 15	97	516 ± 24	89	152 ± 14***	44
Control	348 ± 24	100	681 ± 36	100	431 ± 32	100
αMpT	35 ± 11***	10	131 ± 20***	19	482 ± 15	112
Control	365 ± 11	100	643 ± 39	100	449 ± 45	100
6-Hydroxydopamine	107 ± 6***	29	350 ± 34**	54	444 ± 16	99

* $P < .05$; ** $P < .01$; *** $P < .001$ significantly different from control by Student's t test.

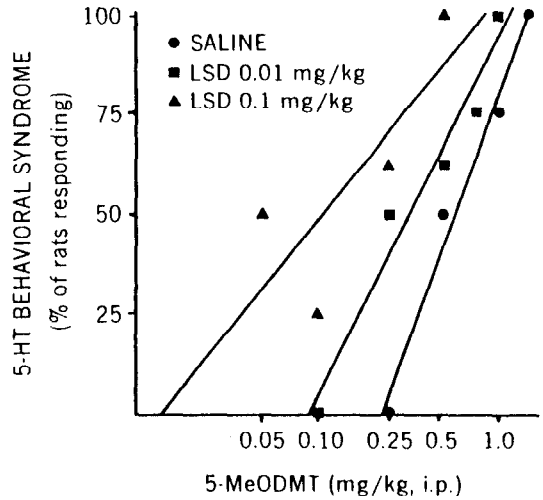

Fig. 1. Enhancement by LSD of 5-MeODMT responses. Eight rats were used per point. Best fit lines drawn by least squares linear regression. Correlation coefficients: saline, $r = 0.99$; LSD, 0.01 mg/kg, $r = 0.98$; LSD, 0.10 mg/kg, $r = 0.79$. The dose of 5-MeODMT needed to elicit an apparent half-maximal response was decreased approximately 2-fold by 0.01 mg/kg of LSD and approximately 5-fold by 0.10 mg/kg of LSD.

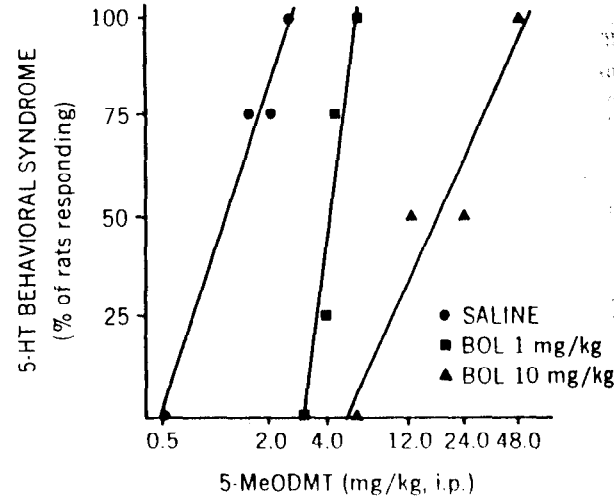

Fig. 3. Displacement of 5-MeODMT dose-response curve by BOL. Saline or BOL was injected 5 min before 5-MeODMT challenge. Four rats were used to establish each point. Correlation coefficients: saline, $r = 0.99$; BOL, 1 mg/kg, $r = 0.96$; BOL, 10 mg/kg, $r = 0.95$. Dose of 5-MeODMT needed to elicit apparent half-maximal responses were increased by BOL (approximately 4-fold by 1 mg/kg and 18-fold by 10 mg/kg).

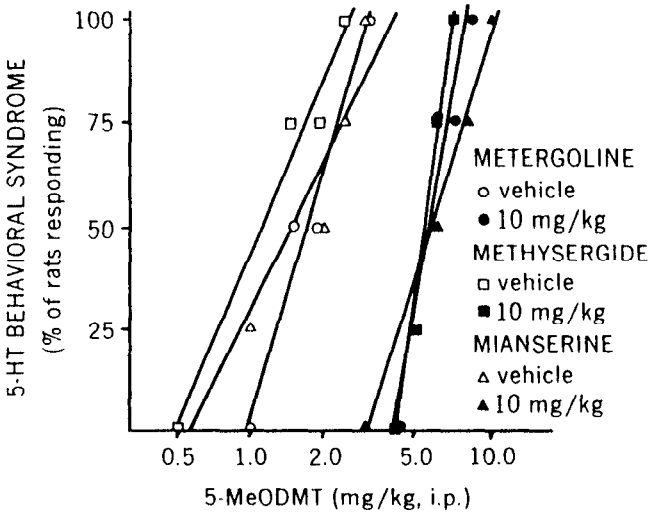

Fig. 2. Effects of presumed 5-HT receptor antagonists on behavioral responses to 5-MeODMT. Methysergide, mianserine or vehicle (saline) was injected 5 min before 5-MeODMT. Metergoline or vehicle (PEG 400) was given 15 min before 5-MeODMT. Four rats were used to establish each point. 5-MeODMT dose needed to produce an apparent half-maximal response was increased 3- to 4-fold by the antagonists.

serotonergic behavioral effects: DMPEA; mescaline; PMA; DMA; TMA; DOM; and DOB. All 7 compounds caused the 5-HT behavioral syndrome. Table 4 shows dose-response relationships for each compound and the concentrations of brain monoamines during the 5-HT behavioral syndrome (10 min after injection). None of the compounds affected whole-brain concentrations of 5-HT or NE ($P > .05$). Mescaline (200 mg/kg) and TMA (120 mg/kg) decreased DA to 88% of control ($P < .01$ and $P < .05$, respectively).

The latency of all syndromes was approximately 5 min. Durations were 15 to 60 min depending on dose. Some qualitative differences in behavioral effects were noted. DMA (60 mg/kg) noticeably increased the rate and depth of respiration. Mescaline (200 mg/kg) caused lethargy and hyperemia of ears and footpads. DMPEA (400 mg/kg) caused convulsions and death, although lower doses evoked the syndrome without producing these effects. Table 4 also includes data showing a general correlation between the hallucinogenic potency of phenethylamines in man and their potency as 5-HT agonists in rats.

Effect of 5-HT depletion. *p*CPA (400 mg/kg i.p.), given 3 days before behavioral testing, reduced 5-HT concentrations to 19% of control ($P < .001$; table 3) and prevented the 5-HT behavioral syndrome caused by PMA (20 mg/kg). However, a higher dose of PMA (80 mg/kg) did evoke the syndrome in similarly pretreated rats. This experiment was repeated in rats that received three injections of *p*CPA, so that 5-HT was approximately 10% of control. In these rats, PMA (80 mg/kg) still evoked the 5-HT behavioral syndrome.

Serotonin concentrations were partially replenished just before behavioral testing in a randomly selected group of *p*CPA-treated rats by injecting the 5-HT precursor, 5-HTP. 5-HTP (30 mg/kg) raised brain 5-HT from 19% of control to 65% in 30 min ($P < .001$; table 3) and restored the behavioral response to PMA (20 mg/kg). *p*CPA pretreatment did not prevent the 5-HT behavioral syndromes caused by mescaline, DOM, DOB, DMA, TMA or DMPEA, indicating direct 5-HT receptor agonist actions of these compounds.

Effect of BOL. BOL (5 mg/kg; 5 min before test compound) prevented the 5-HT behavioral syndromes caused by all indoles and phenethylamines tested at those doses that caused the syndrome in four of four rats (tables 2 and 4). The behavioral blockade by BOL lasted 15 to 20 min. The short duration of blockade was most likely due to the short half-life (~ 1 hr) of BOL in rat brain (Eckert *et al.*, 1978).

Shaking behavior. Shaking behaviors (including head twitches) in rats and mice have been proposed as models of 5-HT receptor activation (Corne and Pickering, 1967; Bédard and Pycock, 1977), although the specificity of the shaking response has been questioned (Drust *et al.*, 1979; Fozard and Palfreyman, 1979). In the course of these experiments, considerable head shaking was observed after DMPEA, mescaline, TMA, DOM and DOB. Fewer head shakes were noted with other phenethyl-

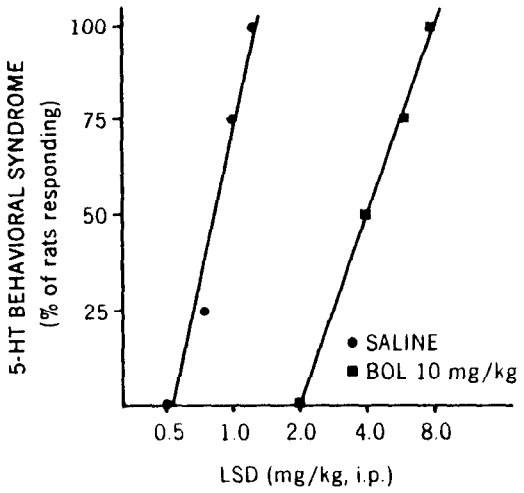

Fig. 4. Displacement of LSD dose-response curve by BOL. Saline or BOL was injected 5 min before LSD. Four rats were used for each point. Correlation coefficients: saline, $r = 0.98$; BOL, 10 mg/kg, $r = 0.99$. BOL increased by a factor of 4 the dose of LSD needed to elicit an apparent half-maximal response.

TABLE 2

Effect of indole hallucinogens on behavior and brain monoamine concentrations

Drugs are listed in order of increasing potency in causing the syndrome. There were four rats in each behavioral group and six in each neurochemical group. Drugs were given i.p. 10 min before sacrifice. Mean control concentrations for three separate assays were: NE 363 ± 16; DA, 592 ± 20; and 5-HT, 490 ± 25 (mean ± S.E.M.; nanograms per gram of frozen tissue).

Treatment	Hallucinogenic Potency[a]	Syndrome Response Ratios[b]	NE[c]	DA[c]	5-HT[c]
mg/kg b.wt.	MU				
Ibogaine	N.D.				
5.0		0/4			
10.0		2/4			
20.0		3/4			
40.0		4/4	94	139***	105
DMT	4				
10.0		1/4			
20.0		3/4			
40.0		4/4	99	103	105
DET	>4				
2.5		0/4			
5.0		1/4			
10.0		4/4	98	114	109
5-MeODMT	>31				
0.5		0/4			
1.0		1/4			
2.0		4/4	96	98	107

[a] Human data are expressed in Mescaline Units (MU); data from Brawley and Duffield (1972); N.D. = no data available.
[b] Number of rats displaying syndrome per number tested.
[c] Percentage of vehicle control value.
*** $P < .001$, significantly different from vehicle control by Student's t test.

ylamines and indoles, even though these compounds evoked the 5-HT behavioral syndrome. Shaking appeared more intense for phenethylamines with methoxy-substituted rings, although the responses were not rigorously tabulated.

Discussion

The results of these experiments indicate that LSD is a direct acting central 5-HT agonist *in vivo*, whereas BOL is a central 5-HT antagonist *in vivo*. The evidence is as follows: 1) LSD, 1 mg/kg i.p. or more, caused the 5-HT behavioral syndrome. This result agrees with observations of others (Kuhn and Appel, 1975; Trulson and Jacobs, 1976); 2) neither reduction of catecholamine concentrations by α-M*p*T or by 6-hydroxydopamine, nor reduction of 5-HT by *p*CPA or by 5,7-DHT prevented the 5-HT behavioral syndrome evoked by LSD; 3) LSD in low doses (10 and 100 μg/kg i.p.) shifted the dose-response curve for 5-MeODMT, a 5-HT receptor agonist, to the left. No antagonist actions of LSD were detected in the dose range of 10 μg/kg through 4 mg/kg; 4) in contrast to LSD, BOL (1 and 10 mg/kg i.p.) shifted the 5-MeODMT dose-response curve to the right, as did the putative 5-HT receptor blockers methysergide, mianserine and metergoline; 5) BOL (10 mg/kg i.p.) also shifted the LSD dose-response curve in parallel to the right, indicating competitive inhibition of 5-HT agonist actions of LSD; and 6) BOL never caused the 5-HT behavioral syndrome throughout a wide dose range (1–100 mg/kg i.p.).

In contrast to the present results with BOL, methysergide, mianserine and metergoline, Haigler and Aghajanian (1974b) reported that the putative 5-HT antagonists, methysergide, metergoline, methiothepin, cyproheptadine and cinanserin, failed to block the effects of iontophoretic 5-HT. Furthermore, Aghajanian (1976) reported that BOL did not block the iontophoretic effects of 5-HT or LSD. These negative findings are difficult to reconcile with the behavioral data obtained in the present studies and with observations that BOL and methysergide, for example, potently displace [^{3}H]-5-HT and [^{3}H]LSD from binding sites in rat brain homogenates (Bennett and Snyder, 1976; Lovell and Freedman, 1976).

Although mechanisms other than 5-HT agonism could account for the leftward shifts of the 5-MeODMT curves by LSD (10 and 100 μg/kg), this is the most likely explanation since LSD alone causes the 5-HT behavioral syndrome at higher doses. In addition, no 5-HT antagonist actions of LSD were detected in a model sensitive to antagonists (*e.g.*, BOL). Caution must be exercised in the design and interpretation of this type of experiment. If a compound shifts the dose-response curve of a 5-HT agonist to the left, but does not cause the syndrome when injected alone, it would be imprudent to conclude that it is a 5-HT agonist. Conceivably, many central nervous system stimulants could shift the curves to the left without involving serotonergic mechanisms. Similarly, any drug which causes

TABLE 3

Effect of *p*CPA and 5-HTP on brain monoamine concentrations

Rats received *p*CPA methylester HCl (400 mg/kg i.p.) or saline; 72 hr later they were injected with 5-HTP (20 mg/kg i.p.) or saline. Rats were sacrificed 30 min after their second injection. Values given are mean concentrations (nanograms per gram of frozen tissue) ± S.E.M. ($n = 4$) or percentage of control (saline + saline).

Treatment	NE		DA		5-HT	
	Conc.	%	Conc.	%	Conc.	%
Saline + saline	347 ± 7	100	590 ± 42	100	429 ± 22	100
*p*CPA + saline	285 ± 3***	82	611 ± 38	104	80 ± 16***	19
*p*CPA + 5-HTP	277 ± 15**	80	596 ± 42	101	280 ± 20*	65

*** $P < .001$, significantly different from *p*CPA + saline group; ** $P < .01$; *** $P < .001$, significantly different from control by Student's t test.

TABLE 4

Effect of phenethylamine analogs on behavior and brain amine concentrations

Drugs are listed in order of increasing potency in causing the syndrome. There were four rats in each behavioral group and six in each neurochemical group. Drugs were given i.p. 10 min before sacrifice. Mean control concentrations for five separate assays were: NE, 385 ± 11; DA, 630 ± 19; and 5-HT, 537 ± 27 (mean ± S.E.M.; nanograms per gram of frozen tissue).

Treatment	Hallucinogenic Potency[a]	Syndrome Response Ratios[b]	NE[c]	DA[c]	5-HT[c]
mg/kg b.wt.	MU				
DMPEA	<0.2				
100.0		1/4			
200.0		3/4			
400.0		4/4	96	105	Interference
Mescaline	1.0				
80.0		0/4			
120.0		2/4			
200.0		4/4	99	88**	103
TMA	2.2				
40.0		0/4			
80.0		1/4			
120.0		4/4	95	88*	108
DMA	8				
20.0		0/4			
40.0		1/4			
60.0		4/4	98	96	107
DOM	80				
10.0		0/4			
20.0		3/4			
40.0		4/4	96	112	100
PMA	5				
5.0		0/4			
10.0		3/4			
20.0		4/4	106	117	107
DOB	400				
2.5		0/4			
5.0		2/4			
10.0		4/4	92	103	106

[a] Human data are expressed in Mescaline Units (MU) (Shulgin *et al.*, 1969, 1971).

[b] Number of rats displaying syndrome per number tested.

[c] Percentage of vehicle control value.

* $P < .05$; ** $P < .01$, significantly different from vehicle control by Student's *t* test.

lethargy (*e.g.*; αM*p*T) probably would shift the curve to the right. Interpretation of the latter as catecholamine modulation of serotonergic mechanisms, for example, would be unwarranted.

Our results with LSD and BOL in rats are consistent with what is known about the relationship between these drugs in man. LSD is hallucinogenic but BOL is not (Cerletti and Rothlin, 1955). In addition, BOL has been reported to block LSD hallucinations (Bertino *et al.*, 1959). By way of comparison, our behavioral results indicate that LSD is a 5-HT receptor agonist but BOL is not. Moreover, BOL blocks the 5-HT agonist effects of LSD.

Experiments with indole and phenethylamine analogs indicate that all hallucinogens tested cause the 5-HT behavioral syndrome without greatly increasing brain 5-HT concentrations as does 5-HTP (Sloviter *et al.*, 1978a). Studies on the mechanism by which these compounds activate 5-HT receptors indicate that, with the exception of PMA, all of the hallucinogens evoked the 5-HT behavioral syndrome by a direct agonist effect. This mechanism is inferred from observations that depletion of endogenous 5-HT by *p*CPA did not prevent the behavioral effects of these compounds. These data do not exclude an additional action, *i.e.*, endogenous 5-HT release. We conclude that PMA acts primarily by releasing endogenous 5-HT, since *p*CPA pretreatment prevented the PMA syndrome and 5-HTP reinstated it. Other workers (Menon *et al.*, 1976; Tseng *et al.*, 1976) arrived at the same conclusion about PMA by using different methods. High doses (80 mg/kg) of PMA evoked the 5-HT syndrome in rats whose brain 5-HT was reduced to 10% of control. Although the possibility that high doses of PMA caused the syndrome by releasing residual 5-HT cannot be ruled out, it seems more likely that PMA has a direct agonist action in addition to releasing 5-HT. This conclusion is supported by the observation that similarly depleted rats did not display the syndrome after equivalent doses of amphetamine, a compound that produces the syndrome exclusively by 5-HT release (Sloviter *et al.*, 1978b). Andén *et al.* (1974), by using a spinal reflex model, also concluded that PMA and DOM stimulated 5-HT receptors but that DMPEA (50 mg/kg) and mescaline (50–100 mg/kg) did not. Our results show that, as might be predicted from their low hallucinogenic potency, higher doses of mescaline and DMPEA (100–200 and 200–400 mg/kg, respectively) are needed to elicit serotonergic effects. These results serve to underscore the absolute necessity for complete dose-response experiments before concluding that a compound is not a 5-HT agonist.

Just how relevant the 5-HT behavioral syndrome in rats is to hallucinations in man remains argumentative. What emerges from this work with hallucinogens as a class of drugs is that the interspecies behavioral responses to the drugs have similar pharmacological profiles. The two behaviors, if not congruent, at least run in parallel. All of the compounds tested in these experiments cause hallucinations in man (Shulgin, 1976) and cause the 5-HT behavioral syndrome in rats; this is not to say that the reverse is necessarily true, *i.e.*, that all compounds which cause the 5-HT behavioral syndrome in rats must be hallucinogenic. Overall, the potency of serotonergic effects in rats was well correlated with hallucinogenic potency in man (tables 2 and 4). In addition, BOL, which reportedly attenuates LSD effects in man, blocked the 5-HT behavioral syndrome caused by LSD and all the other hallucinogens tested. Thus, these studies support the hypothesis that hallucinogens, whether of lysergic acid, indolealkylamine or phenethylamine structure, share a common mechanism of action (Snyder and Richelson, 1968).

If 5-HT receptor activation mediates hallucinations in man, as proposed originally by Woolley (1962), treatments that simply increase brain 5-HT concentrations might be expected to cause hallucinations. However, clinical studies with tryptophan (Carroll, 1971) or 5-HTP (Wyatt *et al.*, 1971; Carroll, 1971) have not revealed hallucinations as a frequent adverse effect of 5-HT precursors. Similarly, Grahame-Smith (1971a) showed in rats that large doses of tryptophan caused a relatively small increase in brain 5-HT and no overt behavioral responses. However, when rats received tryptophan plus a monoamine oxidase inhibitor (MAOI), brain 5-HT accumulated and the animals displayed the behavioral syndrome used in these studies. He attributed the behavioral response to the accumulation and "spilling out" of 5-HT onto its receptors. Grahame-Smith (1971a) also observed that reserpine or tetrabenazine greatly potentiated the response in rats to tryptophan plus MAOI, presumably by decreasing amine storage. Subsequently, he tested this drug combination in two depressed patients (Grahame-Smith, 1973). Tryptophan alone or in combination with MAOI did not affect behavior. However, when reserpine was added to the regimen, both patients experienced agitation and

vivid hallucinations. After a drug-free period, the identical regimen was repeated in one patient with the same behavioral results. Although the report was clearly anecdotal, a combination of drugs such as described by Grahame-Smith (1973) might be the only way, by using 5-HT precursors, to stimulate central 5-HT receptors in man to the degree necessary for hallucinogenesis.

Amphetamine in high doses causes an hallucinatory state in humans very similar to paranoid schizophrenia (Angrist and Sudilovsky, 1978). Since amphetamine releases dopamine, the psychotomimetic effect of amphetamine has become one of the main pieces of evidence supporting the dopamine theory of schizophrenia (see review by Meltzer and Stahl, 1976). The observation that levodopa causes paranoia in some Parkinsonism patients (see review by Murphy, 1973) has been taken as additional support for the dopamine theory. However, high doses of amphetamine or levodopa plus MAOI also cause the 5-HT behavioral syndrome by releasing endogenous 5-HT (Sloviter *et al.*, 1978a,b). Furthermore, the *d*-isomer of amphetamine is 2 to 3 times more potent than the *l*-isomer in producing the 5-HT behavioral syndrome (Sloviter *et al.*, 1980), a potency ratio similar to that associated with amphetamine psychosis in humans (Davis and Janowsky, 1973). Conversely, the dopamine agonist apomorphine, which apparently lacks psychotomimetic properties (Lal and De La Vega, 1975; Tamminga *et al.*, 1978), does not produce the 5-HT behavioral syndrome (Sloviter *et al.*, 1978a). In addition, pretreatment of nonschizophrenic subjects for 5 to 16 days with α-methyl-*p*-tyrosine, a catecholamine depletor, prevented the peripheral effects of amphetamine but did not prevent the paranoid psychosis induced by amphetamine (Griffith *et al.*, 1972).

Data from behavioral studies in rats, taken together with conclusions from clinical studies indicating similarities between hallucinogenic and psychotic states (Brawley and Duffield, 1972; Bowers, 1972; Dewhurst and Hatrick, 1972), suggest a unifying serotonin hypothesis of drug-induced hallucinogenesis. Specifically, 5-HT receptor activation in man may mediate some central effects of hallucinogenic and paranoid psychosis-inducing drugs. A possible relationship between 5-HT mechanisms and some signs of endogenous psychosis is implied by this hypothesis but remains conjectural.

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