

Comparative Effects of LSD and Lisuride: Clues to Specific Hallucinogenic Drug Actions

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WHITE, F. J. *Comparative effects of LSD and lisuride: Clues to specific hallucinogenic drug actions*. PHARMACOL BIOCHEM BEHAV 24(2) 365-379, 1986 — This review compares the effects of LSD and its nonhallucinogenic congener lisuride hydrogen maleate (LHM) on various biochemical, behavioral and electrophysiological indices of neuronal function. The underlying rationale is that any differences between the effects of LSD and LHM might be relevant to neuronal actions which are unique and specific to hallucinogenic drugs and thereby provide clues to the neurobiological substrates of hallucinogenesis. In biochemical studies, LHM appears to be very similar to LSD with respect to its actions on monoaminergic (5-HT, DA, NE) systems. The major difference between the two ergots appears quantitative in nature since LHM is more potent than LSD, especially on DA neurochemistry. Needed at the present time are additional comparative studies of LSD and LHM with respect to other biochemical measures, for example on the release of 5-HT and DA and comparisons at more molecular levels such as subcellular compartmentation. Also necessary are more intensive regional analyses on specific subpopulations of 5-HT and DA systems (mesolimbic, mesostriatal and mesocortical). Behavioral studies are relatively uniform in their characterization of the greater DA-ergic activity of LHM as compared to LSD. In particular, the drug discrimination (DD) procedure has indicated a more specific interaction of LSD with 5-HT neuronal systems as compared to LHM and has successfully differentiated the relative roles of 5-HT and DA systems in the behavioral effects of LSD and LHM. Electrophysiological studies have been consistent with both biochemical and behavioral findings with respect to the much greater effect of LHM on DA receptors. In fact, the effects of LSD on DA-containing neurons are both weak and heterogeneous, again indicating a need for more detailed analyses of specific DA projection systems. The greater potency of LHM than LSD on 5-HT containing dorsal raphe neurons has lessened the attractiveness of the once popular theory that hallucinogenic efficacy is related to diminution of impulse flow in 5-HT systems but has also spawned greater interest in the possible role of postsynaptic 5-HT receptors in hallucinogenic drug action. Thus far, the most interesting finding is the ability of LSD and other hallucinogens, but not LHM, to potentiate an excitomodulatory effect of 5-HT in the facial motor nucleus. If such a phenomenon occurs more generally in the CNS, the importance of this finding will be greatly enhanced. Preliminary data is presented which suggests that LSD may also induce such an effect in a limbic forebrain structure, the nucleus accumbens. In a concluding summary, it is proposed that those 5-HT receptors which seem most likely to be involved in the hallucinogenic experience are those at which LSD is active but LHM is not (or is less so) and at which 5-HT antagonists are effective in reducing the LSD effect.

LSD	Lisuride	Hallucinogens	Serotonin neurons	Dopamine neurons	Serotonin receptors
Lysamine receptors		Drug discrimination	Nucleus accumbens		

SINCE Hoffman's serendipitous discovery of the potent hallucinogenic actions of lysergic acid diethylamide (LSD) in 1943 [52], researchers have attempted to elucidate the neuropharmacological changes which cause or, at least, correlate with the behavioral and perceptual manifestations characteristic of the LSD experience. Nevertheless, despite the use of many diverse physiological, pharmacological and behavioral procedures, the mechanisms underlying the complex spectrum of LSD's biobehavioral actions remain undiscerned. Of course, this should not be surprising in view of the myriad components of the LSD "trip" and the gradual unfolding of sequential stages, all of which are likely to result from the interactions of separate and perhaps subtle neurobiological substrates.

Historically, the behavioral effects of LSD have been

linked to the endogenous monoamine neurotransmitters, particularly the indoleamine serotonin (5-hydroxytryptamine, 5-HT), but also to a lesser extent the catecholamines (CA), dopamine (DA) and norepinephrine (NE). The first hypothesis regarding the mechanism of action of LSD was based on antagonism of this amine in isolated smooth muscle preparations [43,114]. Thus, it was proposed that LSD-induced hallucinations might be dependent upon a similar 5-HT antagonism in the central nervous system (CNS). As knowledge of the CNS anatomy and physiology of the monoamines emerged, due primarily to pioneering histofluorescence visualization of amine containing neurons [30], characterization of LSD's neurobiological actions accrued concomitantly, such effects of LSD have proven to be much more complex than the simple 5-HT an-

tagonism observed in smooth muscle and many questions remain as to the exact nature of LSD's interactions with central 5-HT neurons and receptors. Nevertheless, the fact that 5-HT neuronal systems are involved in those actions and resultant hypotheses regarding 5-HT mediation of hallucinogenic efficacy have been widely accepted.

The emphasis on central serotonergic systems as likely mediators of LSD's potent hallucinogenic effects was prompted in the early 1960's by Freedman and colleagues who discovered that LSD increased the whole brain concentrations of 5-HT and decreased the levels of its major metabolite 5-hydroxyindoleacetic acid (5-HIAA) [37, 38, 40, 83]. An important aspect of these findings, as well as subsequent pharmacological analyses, was the inability of brom-LSD (BOL) to mimic the action of LSD. BOL and LSD are nearly equipotent in their effects on peripheral 5-HT systems [22], but unlike LSD, BOL is, at best, only a very weak hallucinogenic agent [17]. This differential hallucinogenic potency of BOL and LSD provided investigators with a valuable tool for dissecting relevant neurobiological substrates (correlates) of hallucinogenic activity. Thus, any central effect of LSD which was mimicked by BOL could be ruled out (at least tentatively) as an accountable mechanism. For example, it has been reported that LSD and other hallucinogens act as antagonists of central H-1 [36] and H-2 [47] histamine receptors, yet BOL is as effective as LSD at both receptors. Therefore, the relevance of these receptors for LSD-induced hallucinosis seems questionable.

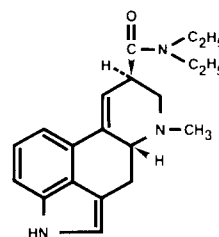
Using the LSD vs. BOL strategy, a variety of CNS effects specific to LSD have been identified over the past two decades [58]. However, an even more powerful lever for prying specific hallucinogenic neuronal substrates has recently become available. The identification of the close structural LSD-congener lisuride hydrogen maleate (LHM) (Fig. 1) as a nonhallucinogenic ergot derivative [48] has been of considerable importance because of its strikingly similar pharmacological profile to LSD. Thus, LHM has been found to mimic many of the CNS effects of LSD and, in most cases, is actually more potent than LSD itself. By systematically comparing the commonalities and differences between the actions of these two ergots, it is possible to identify with greater precision those mechanisms which are likely to be responsible for components of the LSD experience. The purpose of the present discussion is to provide a review and appraisal of those neuropharmacological assays in which LSD and LHM have been compared directly (with particular emphasis on those systems employed by the author), as well as those systems thus far lacking in precise comparative data. For purposes of organization and clarity, the material has been divided into sections covering biochemical, behavioral and electrophysiological studies.

BIOCHEMICAL STUDIES

Amine Turnover

The comparative biochemical effects of LSD and LHM have been reviewed recently [39]. Therefore, the present discussion will attempt to highlight and update the previous review. The first study which caused researchers to question the theory that 5-HT neuronal systems mediate in some way the hallucinogenic property of LSD was performed by Pieri *et al.* [74] who compared the biochemical changes occurring in rat brain following peripheral administration of LSD and LHM. These two compounds produced strikingly similar effects, particularly a decrease in 5-HT turnover, except that

LYSERGIC ACID DIETHYLAMIDE (LSD)



LISURIDE HYDROGEN MALEATE (LHM)

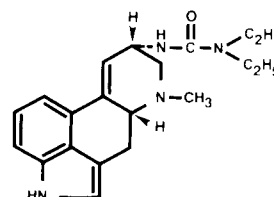


FIG. 1 Chemical structures of LSD and LHM

LHM-induced changes were somewhat more pronounced than those of LSD. On the basis of these results, Pieri *et al.* [74] concluded that "the biochemical changes induced by both lisuride and LSD may solely represent an epiphenomenon unrelated to the hallucinosis." In addition to the common ability of LSD and LHM to increase concentrations of 5-HT and decrease 5-HIAA, these two ergots also caused similar increases in DA levels and decreases in the levels of the DA metabolite dihydroxyphenylacetic acid (DOPAC). Moreover, both LSD and LHM increased NE turnover [74]. The major difference between LSD and LHM was a quantitative one, LHM was more potent than LSD, especially with regard to changes in the CA's. Similar results have been obtained by other investigators [62-64]. For example, using an *in vivo* method of measuring the immediate precursors of 5-HT and DA, i.e., 5-hydroxytryptophan (5-HTP) and dihydroxyphenylalanine (DOPA), after inhibiting aromatic amino acid decarboxylase with 3-hydroxybenzylhydrazine, Kehr [62] found that both LHM and LSD reduced the synthesis and metabolism of 5-HT and, whereas LHM was a potent DA agonist (inhibited DA synthesis), LSD was only a weak DA agonist and, at higher doses, showed DA antagonist activity, i.e., increased DA synthesis.

There are several biochemical effects of LHM which are not shared by LSD. First, LHM antagonizes methiothepin-induced increases in 5-HT turnover [74]. Second, LHM decreases DOPA accumulation in DA-rich brain regions [74]. Third, LHM reduces concentrations of the DA metabolite homovanillic acid (HVA) whereas LSD tends to increase HVA levels [64]. However, not yet as evident are biochemical effects of LSD that are not mimicked by LHM, such effects may be of particular interest in determining hallucinogenic efficacy.

Receptor Binding and Adenylate Cyclase

Both LSD and LHM displace ³H-spiroperidol from DA receptors in rat striatal membranes at low concentrations

[41,55] In rabbit caudate, LHM displaces ^3H -ADTN (2-amino-6,7-dihydro-1,2,3,4-tetrahydronaphthalene) [84], which labels DA receptors [28], and ^3H -LSD [84] which labels both DA and 5-HT receptors [20]. In rat frontal cortex, LHM potentially displaces the three serotonergic ligands, ^3H -LSD, ^3H -5-HT and ^3H -spiroperidol [55,84]. Conversely, LSD potentially displaces ^3H -LHM binding in both striatum and frontal cortex [15]. Thus, it is apparent that LSD and LHM are strikingly similar with respect to receptor activity as determined by *in vitro* binding assays.

Both LSD and LHM have been shown to stimulate a 5-HT sensitive adenylate cyclase in frontal cortex and this stimulation is antagonized by the DA and 5-HT antagonist molindone [7,84]. Some researchers have reported that LSD [7, 31, 98], but not LHM [74,84], stimulates DA-sensitive adenylate cyclase activity in the striatum. Others have reported that LHM can stimulate DA-sensitive cyclase in striatal homogenates [11] and slices [85]. Both LSD and LHM antagonize DA-stimulated cyclase activity [31, 74, 84, 98].

Release Experiments

In a recent interesting report, Hetey *et al* [49] have shown that LSD and other hallucinogens (mescaline, DMT), but not LHM, dose-dependently inhibit the K^+ -evoked ^3H -DA release from crude synaptosomal fractions of rat nucleus accumbens (NAc). Because these effects were blocked by both haloperidol and methiothepin, it was postulated that the effect of the hallucinogens depended upon both DA and 5-HT receptors located presynaptically on DA nerve terminals [49]. While this is an intriguing finding suggesting a common effect of structurally dissimilar hallucinogens which is not mimicked by LHM, the lack of effect of LHM is surprising since it suggests that LHM does not stimulate presynaptic DA receptors on DA nerve terminals (autoreceptors). Although a similar conclusion was reached by Keabian and Keabian [61] who found that LHM did not inhibit tyrosine hydroxylation *in vitro*, other studies have shown that LHM does inhibit DA synthesis under certain *in vitro* assay conditions [93]. Moreover, several reports have indicated that LHM is a relatively potent stimulant of DA autoreceptors *in vivo* [62, 67, 99, 100, 110, 112]. Direct evidence for LHM-induced stimulation of the DA autoreceptors which modulate impulse-flow in DA neurons is presented below (see Electrophysiological Studies).

Thus far lacking and sorely needed are comparative studies of LSD and LHM on 5-HT release and its controlling mechanisms, as well as additional studies on DA release, both *in vitro* and *in vivo*, perhaps with push-pull cannulae, *in vivo* voltammetry or intracerebral dialysis. Moreover, comparative studies at more molecular levels such as subcellular compartmentation and nerve terminal membranes, of both DA and 5-HT neurons, would be informative [39]. Also needed are regional analyses of LSD's and LHM's effects on specific subpopulations of 5-HT and DA systems (cortical, limbic, striatal, etc.). Comparisons of LSD- and LHM-induced alterations of NE systems have thus far been limited and additional detailed studies also seem warranted.

BEHAVIORAL STUDIES

DA-Dependent Behaviors

Over the past twenty years an enormous amount of behavioral research has been conducted with LSD, not only to

catalogue the effects of this extremely potent compound on behavior, but also to identify the neuropharmacological mechanisms underlying such changes. In conducting such experiments, behavioral pharmacologists have relied on a vast array of disparate behavioral techniques and animal species. Probably the simplest and most frequently used procedures in behavioral pharmacology involve observing drug-induced changes in gross behavior, typical measures include general motor activity and repetitive, stereotypic behaviors (gnawing, licking, etc.). In fact, these behaviors have generally been thought to indicate an increase in DA receptor activity [34,78]. Since LSD has been reported to cause both of these behaviors, effects which are reversed by DA antagonists, it was suggested early on that LSD acts as a DA agonist [32,35]. However, one consistent aspect of these experiments is that the doses of LSD which produce such effects are *extremely* high (5.0–10.0 mg/kg) and have little, if any, relevance to doses which produce effects on the firing of CNS neurons (0.02–0.10 mg/kg) or induce hallucinosis in man (0.0025–0.005 mg/kg). Moreover, careful examination of the descriptive accounts of the LSD-induced stereotypies indicate that many of the individual behaviors (head weaving, tremor, splayed hindlimbs) are now considered to be components of a 5-HT syndrome (see below).

LHM exerts a bi-phasic effect on motor behavior in rodents [67,99]. At low doses (0.1 mg/kg) this compound, like apomorphine, produces a decrease in activity [67,99], presumably by activating DA autoreceptors [31]. At higher doses (>0.1 mg/kg), LHM causes increases in locomotor activity and stereotypies, all of which are blocked by DA antagonists [54]. Clearly, with respect to motor activity and stereotypy, LHM is a more potent DA agonist than LSD.

Another behavioral model for studying DA action is rotational behavior induced by DA agonists in rats with unilateral 6-hydroxydopamine (6-OHDA)-induced lesions of the substantia nigra [96]. Such turning behavior is contralateral to the lesioned side after a direct DA agonist, but is ipsilateral after an indirect DA agonist. LSD has been shown to induce contralateral turning in this paradigm and the rotation is blocked by DA antagonists such as haloperidol or pimozide [75]. In addition, LSD increases locomotor activity in 6-OHDA lesioned rats. These results have thus strengthened the view that LSD acts as a DA agonist [65,75]. However, both the sensitivity and specificity of the rotational assay are somewhat questionable because the doses of LSD that reliably produce these effects are relatively high (0.5 to 2.0 mg/kg) and the DA receptors, through which this behavioral episode is mediated, are not only supersensitive [97] but also nonspecific [26]. Furthermore, LSD-induced circling has not always been replicated [70,77]. LHM also induces contralateral circling indicative of a direct acting DA agonist [42,76], in fact, LHM is at least five times more potent than apomorphine in this model [42].

Pieri *et al* [76] compared directly the rotational behavior induced by LSD, LHM, and apomorphine in rats with unilateral nigrostriatal lesions produced by either 6-OHDA or 5,6-dihydroxytryptamine (5,6-DHT), a neurotoxin which depletes 5-HT as well as DA [16]. The rotation induced by LHM or LSD was more pronounced in rats with 6-OHDA lesions than in those with 5,6-DHT lesions. There were no differences between the two lesion groups with respect to apomorphine-induced circling. The authors suggested that this was an indication of serotonergic involvement in the actions of LSD and LHM because 5,6-DHT depletes both 5-HT and DA, and 5-HT modulates turning behavior in a

direction opposite to DA [29,70]. Thus the net effect of stimulating two neuronal systems, both with supersensitive receptors (5,6-DHT group), was an overall reduction in rotation as compared to the apomorphine group (DA stimulation alone) or to the rats with only DA depleted (6-OHDA group). LHM was about 10–20 times more potent and considerably longer acting than LSD [76]. Haloperidol completely blocked the LHM circling but only partially diminished LSD rotation, again demonstrating the greater dopaminergic activity of LHM and the fact that LSD-induced circling involves non-DA mechanisms. Both LHM and LSD also counteracted the catalepsy induced by the neuroleptic prochlorperazine, another effect thought to reflect DA receptor stimulation [76], LHM was also more potent and longer acting than LSD in this model.

5-HT Dependent Behaviors

Another set of drug-induced behavioral changes in rats has been suggested to indicate a specific interaction with 5-HT receptors [46,57], and has thus been termed the "serotonin syndrome" [57]. This syndrome is distinguishable from the stereotypy induced by DA agonists by the appearance of head weaving, reciprocal forepaw treading, hind limb abduction, resting tremor, and Straub tail (raised and rigid position). The syndrome is reliably produced by inhibition of monoamine oxidase (MAO) in conjunction with injections of either of the amino acid precursors of 5-HT, L-tryptophan or 5-HTP [46]. In addition, drugs which act as central 5-HT agonists produce the syndrome, including LSD, 5-methoxy-N,N-dimethyltryptamine (5-MeODMT) and quipazine [57, 90, 95].

By comparing the ability of LHM and LSD to produce the "serotonin syndrome," Silbergeld and Hruska [87] found that both compounds induced signs of the syndrome, but LHM was more potent. Pretreatment with haloperidol potentiated and prolonged the LSD-induced syndrome but had no effect on LHM-induced behaviors, this may occur because DA receptor blockade decreases the DA agonist effect of LSD and thus allows a clearer expression of the serotonin syndrome. The failure to observe the same interaction with LHM was explained by the greater potency of LHM for DA receptors [87]. The 5-HT antagonist methysergide partially blocked the effects of LSD, but not those of LHM. Unfortunately, complete dose-response analyses with 5-HT and DA blockers were not performed and more specific 5-HT antagonists were not studied. Again, one must view this behavioral syndrome with caution since the effective doses of both LSD (1.0–2.0 mg/kg) and LHM (1.0–1.5 mg/kg) were extremely high as compared to most behavioral test systems (below).

The Limb-Flick Model

The ability of LSD and other hallucinogens to elicit limb-flicking (LF) and abortive grooming (AG) in cats has been proposed as a specific animal behavior model for hallucinogenic drug action [59]. However, upon closer scrutiny, it has been revealed that this model, like most, is not specific to hallucinogens [106]. Nevertheless, this behavioral model has proven quite useful for simultaneous behavioral and electrophysiological investigations of LSD's effects [50, 92a]. In comparing LHM and LSD in this model, most studies have found that LHM is at least as potent as LSD in eliciting these behaviors [50, 106, 107], actually, we have found LHM to be about four times more potent than LSD

TABLE 1
ANTAGONISM OF THE LIMB-FLICK (LF) RESPONSE ELICITED BY
LSD OR LHM*

Antagonist	Dose (mg/kg)	LSD (0.08 mg/kg)	LHM (0.02 mg/kg)
No antagonist	—	49.0 ± 12.2	50.2 ± 16.8
Haloperidol	0.1	22.5 ± 7.2	28.4 ± 11.7
Haloperidol	0.5	6.0 ± 3.4†	1.0 ± 0.4†
Pizotifen	5.0	0.5 ± 0.3†	6.2 ± 2.3†

*Data are presented as the mean number of LF/hour ± SEM (n=6 in all experiments)

†Significantly less than LSD or LHM alone ($p < 0.05$)

(Table 1). Pharmacological investigations into neuronal mechanisms responsible for LSD and LHM induced LF/AG have demonstrated that although the 5-HT antagonist pizotifen (BC-105) blocked the effects produced by LSD [50,107], the DA antagonist haloperidol was also effective [92a, 107]. Moreover, we found that both of these antagonists also prevented LHM-induced LF [107]. Interestingly, Jacobs and co-workers reported that the 5-HT antagonist mianserin blocked the LF/AG response induced by LSD but not that induced by LHM [50]. Whether this discrepancy is due to the different 5-HT antagonists employed is an important matter worthy of future study. Nevertheless, the fact that LSD and LHM are so similar in this model and the effects of both ergots can be blocked by both 5-HT and DA antagonists casts some doubt on the utility of this model for distinguishing specific neuronal mechanisms relevant for hallucinatory activity [107].

Hallucinogen-Induced Limb-Jerking in Monkeys

Schlemmer and Davis [86] have recently reported that hallucinogenic drugs produce several behavioral effects in the monkey (stumptail macaques), among the most interesting were two emergent behaviors, limb-jerking and body shaking. These behaviors are almost never seen in undrugged monkeys but are induced in a dose-dependent manner by a variety of hallucinogenic drugs, LSD (as usual) being the most potent. Important for the present discussion is the fact that LHM was ineffective at inducing these behaviors [86,86a]. As for antagonism of these behaviors, both 5-HT and DA antagonists effectively reduced the LSD effect although 5-HT blockers were more potent [86]. More detailed study of the receptor mechanisms and locations responsible for this behavior seem warranted.

Disruption of Operant Behavior

In the mid 1960's, Appel and Freedman [8] reported the ability of LSD and other psychotomimetic drugs to disrupt the bar-pressing behavior of rats trained on fixed-ratio (FR) schedules of food or water reinforcement. The disruption of FR responding induced by hallucinogens such as LSD is characterized by an abrupt cessation of responding, the length of which is dose-dependent, and a somewhat less abrupt return to the pre-disruption mode of responses [8]. A considerable amount of work has been conducted with respect to LSD's effects in this paradigm, most of which indi-

cates an almost exclusive role for 5-HT systems in this effect [8, 33, 60, 79]. Recently, Mokler *et al.* [71] compared the effects of LSD and LHM on disruption of FR-40 responding (40 responses are required per reinforcer) and reported that LHM was almost three times as potent as LSD in disrupting FR performance. Interestingly, 5-HT antagonists, but not DA antagonists, blocked the effects of both LSD and LHM [71]. The 5-HT antagonist cinaserin was an exception in that it blocked the effects of LSD but potentiated the effect of LHM, unfortunately, the authors offered no explanations for this rather puzzling finding [71]. For additional information regarding LSD's effects on FR responding, see Sparber [89a].

Drug Discrimination

The drug discrimination (DD) procedure has been particularly successful in the study of neuronal mechanisms underlying the effects of a variety of psychoactive compounds (for recent review see [44]). In this procedure, animals are trained to discriminate between the presence and absence of a drug (drug vs. saline) or the presence of one drug or another drug (drug vs. drug). DD has several advantages over many of the other behavioral procedures described above in that (1) it is exquisitely sensitive to low doses of LSD and other drugs [10], (2) it is relatively specific within pharmacological classes and to particular neuronal actions [10, 13, 44, 82], (3) it is reliable and stable over time [10, 44], and (4) it is the animal behavior which most closely models the subjective experience of drug effects in humans [82].

With respect to the LSD discriminative stimulus (DS) effect or cue, a decade of research has provided substantial evidence that this effect of LSD is mediated by actions at postsynaptic 5-HT receptors. Thus, the LSD cue (1) is readily mimicked by other postsynaptic 5-HT receptor agonists [66, 104], (2) is blocked specifically by 5-HT antagonists [25, 66, 104, 113], (3) is potentiated by pharmacological procedures which deplete 5-HT and increase ³H-LSD binding [10, 108], (4) is discriminably similar to electrical stimulation of 5-HT cell bodies in the dorsal raphe nucleus [51], a manipulation which increases 5-HT release in terminal areas, and (5) is only partially mimicked by direct application of LSD into the dorsal raphe nucleus [82], the site of somatodendritic 5-HT autoreceptors.

We have used the DD procedure and, in particular, a drug vs. drug discrimination to compare and contrast the DS properties of LSD and LHM (Table 2). In the first experiment, two groups of water-deprived male rats were trained to discriminate 0.08 mg/kg of either LSD or LHM from saline in a manner described in detail elsewhere [101–104]. Briefly, rats were injected intraperitoneally (IP) with either the training drug or saline 15 min before being placed in experimental chambers containing two levers. The rats were trained to respond differentially on one of the levers (depending on the solution injected) for water reinforcers. Note that, prior to delivery of the first reinforcer, the only cue the animal could use to determine the correct lever was the drug-induced "state." For this reason, discriminability was always assessed prior to delivery of the first reinforcer or, in test sessions, during extinction periods in which no water was delivered and the session ended after 32 responses had occurred on one of the levers. Following acquisition of the LSD and LHM discriminations, each group of rats was divided into three equal subgroups which were trained to discriminate either 0.02, 0.08 or 0.32 mg/kg of each drug by progressively altering dose [103, 104]. Thus, at the end of training (55 ses-

TABLE 2
COMPARISON OF THE DISCRIMINATIVE STIMULUS PROPERTIES OF LSD AND LHM

Test Drug	LSD vs Saline	LHM vs Saline	LSD vs LHM
Substitution Tests			
5-HT Agonists			
Quipazine	*	†	* for LSD
MK-212	*	†	
5-MeODMT	*	†	
DA Agonists			
Apomorphine	0	*	* for LHM
Lergotril	0	*	
Amphetamine	0	0	
Antagonism Tests			
5-HT Antagonists			
Cyproheptadine	†	0	
BC-105	*	0	
Ketanserin	*	0	
DA Antagonists			
Haloperidol	0	*	
5-HT and Antagonist			
Methiothepin	†	†	

*Complete substitution or antagonism

†Incomplete substitution or antagonism

0—No effect

sions), the rats were accurately discriminating a wide range of doses of LSD or LHM from saline.

Figure 2 shows the results of substitution tests in which different doses of LSD and LHM were administered to assess the similarity of the two ergots. It is apparent that LSD and LHM exerted similar discriminable effects across a wide range of doses. In each group the percentage of drug-lever responding elicited by at least one dose of the novel drug was significant. Nevertheless, particularly noteworthy is the fact that the extent of substitution of the novel drug was usually less than that of the training drug. A similar substitution of LHM in LSD-trained African green vervet monkeys (*Cercopithecus aethiops*) has also been demonstrated recently [71a]. Our data led us to examine the possibility that the DS effects of LSD and LHM might be sufficiently different to allow rats to discriminate between them. Because rats can learn to discriminate quantitative differences in drug effects [14], three groups of rats were trained to discriminate between LSD and LHM at three different potency ratios (0.02, 0.04 or 0.08 mg/kg of LHM vs. 0.08 mg/kg of LSD), chosen on the basis of the previous experiments. Otherwise, the methods were the same as those described previously except that an FR 16 schedule was used.

Each of the three groups readily learned to discriminate LSD from LHM. The results of substitution tests with saline, LSD, LHM, the DA agonist apomorphine (APO), and the 5-HT agonist quipazine (QPZ) are shown in Fig. 3. In the 0.08 mg/kg LHM group, the discrimination seemed to be based on the quantitative difference of amount of drug effect, i.e., at equivalent doses, LHM is much more potent than LSD, thus, during tests with a relatively high dose of any drug, responding occurred primarily on the LHM-appropriate lever whereas during tests with low drug doses,

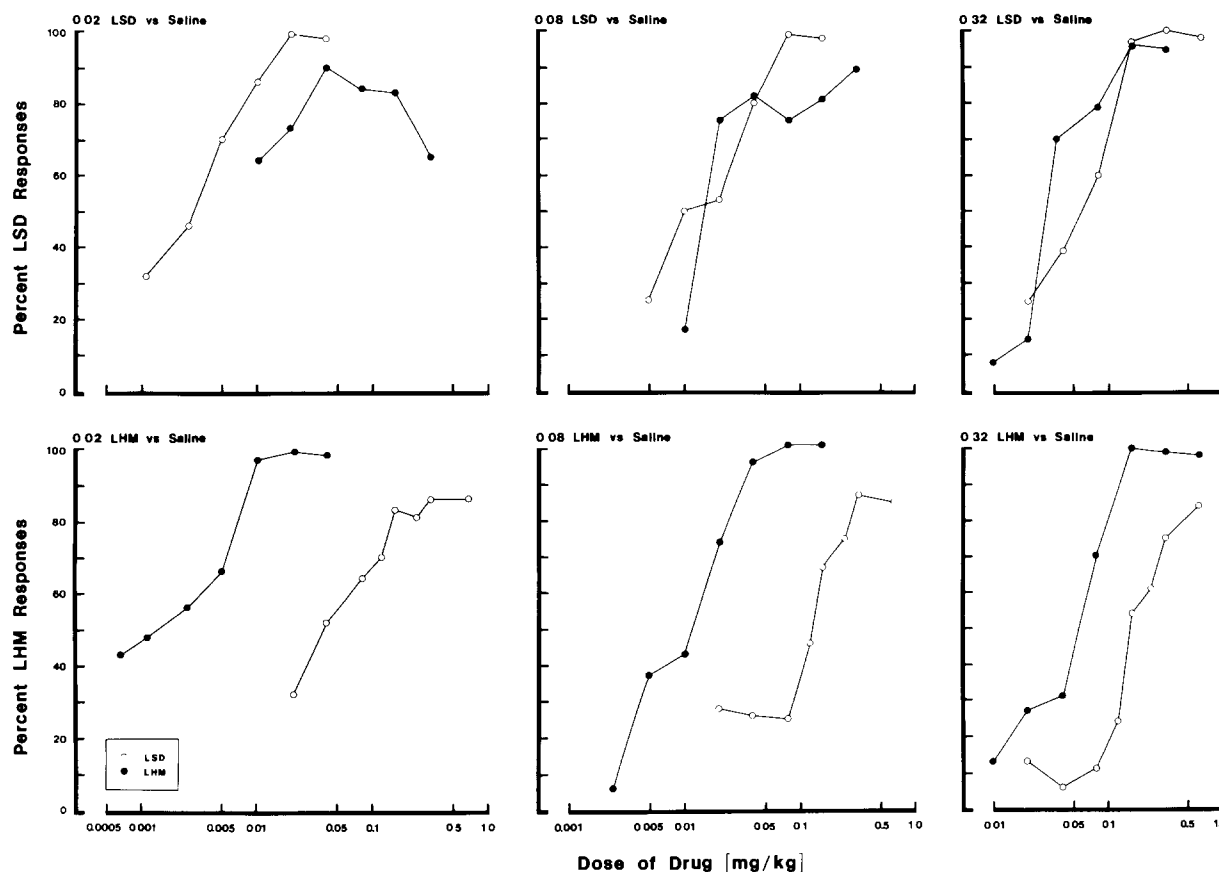


FIG 2 Results of substitution tests with LSD and LHM in groups of rats trained to discriminate one of three doses (0.02, 0.08 or 0.32 mg/kg) of either LSD (top panel) or LHM (lower panel) from saline. Asterisks represent significant substitutions. Reprinted from [102] with permission. (Copyright by the AAAS)

most responding occurred on the LSD-appropriate lever. In contrast, in the other groups, the discriminations were based on *qualitative* differences between the effects of LSD and LHM, i.e., during saline tests and tests with low doses of LSD, choice behavior was not under stimulus control. As the dose of LSD increased, the percentage of LSD lever responding increased to above chance levels. Discrimination of all doses of LHM was near perfect. As the dose of QPZ increased, rats responded as though they had received LSD, as the dose of APO increased, they responded as though they had received LHM.

Thus, the effects of LSD and LHM were sufficiently different to enable rats to discriminate between them. Observations that the 5-HT agonist QPZ elicits LSD-appropriate responding whereas the DA agonist APO elicits LHM-appropriate responding suggest that the DS effects of LSD are mediated primarily by 5-HT receptors whereas the DS effects of LHM are mediated primarily by DA receptors. This interpretation is supported by our findings that (1) 5-HT agonists substitute completely for LSD but only partially for LHM, (2) 5-HT antagonists block the LSD cue but not the LHM cue, (3) DA agonists substitute completely for LHM but not at all for LSD, and (4) DA antagonists block the LHM cue but not the LSD cue (see Table 2). This is not meant to imply that LSD and LHM act *only* at 5-HT and DA receptors, respectively, but that the DS effects of these

drugs are mediated *primarily* by actions on one or the other of these neuronal systems. These data present striking evidence that previously reported quantitative differences between the neuronal actions of LSD and LHM can result in qualitative differences in the discriminable "states" produced by these ergots. Thus, our results parallel those seen in humans in that LHM exerts much greater potency as a DA agonist (anti-Parkinsonian effects) and does not produce LSD-like hallucinogenic reactions [45].

With respect to the possible involvement of NE neuronal systems in the LSD and LHM cues, previous studies have demonstrated that NE is not involved in the LSD cue since it is neither blocked nor mimicked by either α -adrenergic (phentolamine) or β -adrenergic (propranolol) antagonists [66]. Nevertheless, biochemical measures indicate effects of both LSD and LHM on NE turnover, moreover, LHM exerts other effects which are consistent with both α - and β -adrenergic antagonism [15, 27, 62]. To investigate this possibility more directly the effects of selective α_1 and α_2 agents were studied in rats trained to discriminate either LSD (0.08 mg/kg) or LHM (0.04 mg/kg) from saline as described above. In substitution tests, the α_2 blocker yohimbine produced a dose-related increase in both LSD and LHM lever responding which was considerably more evident in the LHM trained rats (Table 3). Neither the α_1 antagonist prazosin nor the β antagonist propranolol

elicited significant LHM or LSD lever responding (Table 3). Thus, these results suggest that α_2 -adrenoceptor antagonism may play a role in the DS effects of LHM, but is less likely to be involved in the LSD cue.

Summary of Behavioral Studies

In contrast to the available biochemical data, behavioral research with direct LSD vs LHM comparisons is more extensive and thorough. It is evident from the available studies that LSD and LHM exert strikingly similar effects on "5-HT-related" behaviors but that LHM is a much more potent elicitor of "DA-dependent" behaviors. In fact, upon review of the available data, there is little compelling behavioral evidence that LSD acts as a DA agonist when administered at reasonable doses in intact (i.e., unlesioned) animals. We have recently found that relatively low doses of LSD partially mimic the DS properties of apomorphine, indicating that DA agonist effects of low LSD doses can be detected when rats are trained to attend to such a neuronal action, i.e., are trained to discriminate a direct DA agonist [53]. Interestingly, we also found that this effect of LSD was blocked to a greater extent by 5-HT antagonists than by DA antagonists, suggesting that the effect may be secondary to 5-HT receptor activation [10,53]. With respect to distinguishing specific LSD induced behaviors and underlying mechanisms, the DD paradigm has been most successful in identifying differences between LSD and LHM; thus, it is obvious that the DS effects of LSD rely primarily on direct postsynaptic 5-HT receptor activation (above) whereas the DS effects of LHM rely primarily on its actions as a direct DA receptor agonist. Among the other interesting behavioral comparisons of LSD and LHM is the finding that the FR-40 disruption caused by these ergots is blocked only by 5-HT antagonists [71]. To date, this seems to be the only effect of LHM (at least at reasonable doses) that is not blocked by DA antagonists, suggesting that the particular pattern of disruption caused by LSD, LHM and various hallucinogenic drugs (pausing) may be a specific reflection of 5-HT receptor activation. Thus, additional studies should attempt to identify the specific types and locations of the 5-HT receptors involved in LSD and LHM induced FR disruption.

ELECTROPHYSIOLOGICAL STUDIES

5-HT Systems

Perhaps the most thoroughly characterized physiological effect of LSD is the ability of very low doses to reduce the firing rate of 5-HT containing neurons in the midbrain dorsal raphe nucleus [4]. These predominantly inhibitory neurons fire in a slow regular rhythm and thus keep the majority of their postsynaptic target cells under tonic inhibition [1,6]. LSD, when applied systemically (IV) in small doses (0.01–0.02 mg/kg) or when applied directly onto the raphe soma by microiontophoresis, produces an abrupt inhibition of the firing rate of these cells [4–6]. This in turn causes an increase in activity of the postsynaptic target cells due to the release of inhibition. Psychoactive congeners of LSD, other hallucinogenic drugs and agents which increase synaptic availability of 5-HT (uptake inhibitors, precursors, monoamine oxidase inhibitors) inhibit these raphe cells; potency of the hallucinogens in this regard is similar to their behavioral potency [6].

Aghajanian and colleagues [5] have also shown that the postsynaptic "target" cells of the raphe nuclei, located in various brain regions (lateral geniculate nucleus, amygdala),

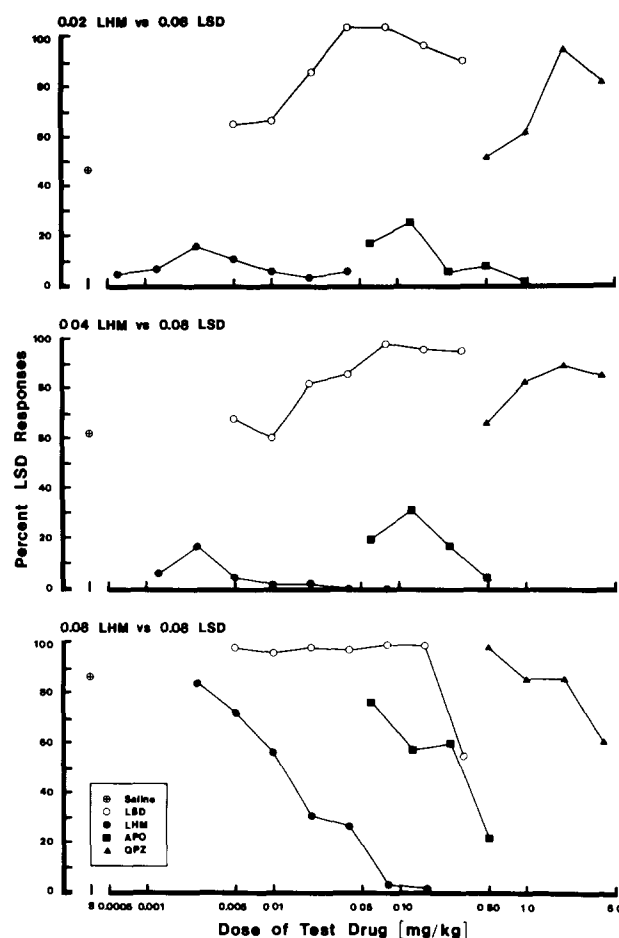


FIG 3 Results of substitution tests with LSD, LHM, quipazine (QPZ) and apomorphine (APO) in rats trained to discriminate 0.08 mg/kg LSD from either 0.02 mg/kg LHM (top panel), 0.04 mg/kg LHM (middle panel) or 0.08 mg/kg LHM (bottom panel). Note that zero percent LSD responses is equivalent to 100 percent LHM responses. Asterisks represent significant substitution of QPZ for the LSD cue, or significant substitution of APO for the LHM cue ($p < 0.05$, t -test for correlated measures). Reprinted from [102] with permission. (Copyright by the AAAS.)

are much less responsive to LSD than are the raphe cells. Therefore, they have proposed that the hallucinogenic effects of LSD may result from this preferential agonistic effect at 5-HT autoreceptors located in the somatodendritic regions of the 5-HT containing raphe neurons [5], reasoning that the preferential inhibition of 5-HT cells causes disinhibition of postsynaptic target cells. In contrast, non-hallucinogenic compounds which suppress 5-HT cells (5-HT, 5-HTP) also potentially inhibit the postsynaptic neurons thereby preventing "disinhibition".

Like LSD, LHM produces an abrupt, dose-dependent suppression of serotonergic neurons in the dorsal raphe [81,100]. In fact, in a comparative study, LHM was found to be 5–10 times more potent than LSD in selectively inhibiting the firing rate of these cells [81], both intravenous and microiontophoretically applied LHM were potent in this regard. On the basis of the molar intravenous dose required to completely inhibit cellular activity in the raphe, LHM is the most

TABLE 3
RESULTS OF SUBSTITUTION TESTS WITH ADRENERGIC AGENTS IN RATS
TRAINED TO DISCRIMINATE LSD (0.08 mg/kg) OR LHM (0.04 mg/kg) FROM SALINE*

Test Drug	Dose (mg/kg)	LSD-Rats	n/N†	LHM-Rats	n/N†
LSD	0.08	98 ± 2	8/8	—	—
LHM	0.04	—	—	99 ± 1	8/8
Saline	—	1 ± 1	8/8	2 ± 1	8/8
Propranolol	5.0	4 ± 2	8/8	3 ± 1	8/8
	10.0	6 ± 3	8/8	12 ± 5	6/8
	20.0	15 ± 8	4/8	9 ± 6	3/8
Phentolamine	5.0	8 ± 3	8/8	4 ± 2	8/8
	10.0	6 ± 2	6/8	10 ± 4	6/8
Prazosin	1.0	2 ± 1	8/8	4 ± 2	8/8
	2.0	3 ± 1	8/8	14 ± 6	8/8
	4.0	12 ± 4	7/8	31 ± 12	7/8
	8.0	21 ± 6	5/8	24 ± 12	4/8
Yohimbine	1.0	0	8/8	20 ± 6	8/8
	2.0	14 ± 8	8/8	46 ± 9	8/8
	4.0	56 ± 12	7/8	67 ± 12	8/8
	8.0	31 ± 14	6/8	79 ± 8	7/8

*All data are presented as the percentage of responses on the drug-lever

†n/N refers to the number of rats responding out of those tested

potent drug described to date [81]. These results provide additional evidence inconsistent with the 5-HT autoreceptor hypothesis of hallucinogenic drug action. However, unlike LSD, LHM is quite potent at inhibiting the firing of amygdala neurons which receive a dense 5-HT innervation (Wang and Aghajanian, unpublished results), a finding which is in accord with the preferential autoreceptor hypothesis of hallucinogenic activity.

More damaging evidence for the autoreceptor hypothesis of hallucinogenic drug action has been provided by a recent series of experiments in which dorsal raphe activity and behavioral measures were simultaneously monitored in awake, freely moving cats [94]. These experiments revealed that the time course of the behavioral effects of LSD (LF/AG, see above) does not correlate with inhibitory effects of LSD in the dorsal raphe. In addition, although the behavioral effects of LSD exhibited tolerance following repeated administration, such was not the case for inhibition of dorsal raphe activity [94]. Although these results argue against actions at the dorsal raphe as the primary mechanism of LSD-induced hallucinosis, one must take into account the possible lack of appropriateness of the LF/AG cat model as an indicator of hallucinogenic efficacy (above). Perhaps equally damaging to the autoreceptor hypothesis is the recent finding that the 5-HT agonist quipazine, which is apparently nonhallucinogenic [72,105] possesses a post/presynaptic efficacy ratio (for inhibiting 5-HT neurons and neurons in the lateral geniculate nucleus, respectively) that is similar to that of LSD [18].

In view of the above problems with the presynaptic 5-HT receptor hypothesis of LSD's hallucinogenic potency, and the behavioral evidence supporting an important role of

postsynaptic 5-HT receptors in hallucinogenic activity [102], electrophysiologists have turned their attention to postsynaptic 5-HT receptors as potential sites of specific hallucinogenic actions. In an elegant series of experiments, McCall and Aghajanian [69] have shown that LSD and other hallucinogens, but not LHM, can potentiate the excitomodulatory effects of 5-HT on glutamic acid-induced excitations in the rat facial motor nucleus (see [68a] for detailed summary and references). Moreover, this is an effect that is blocked by 5-HT antagonists, a finding which is in concert with the behavioral evidence discussed above.

It is difficult to envision how actions of LSD on motor neurons could be involved in the complex hallucinatory episodes induced by LSD. However, if such actions of LSD occur more generally at other brain sites, perhaps in limbic, visual or cortical areas, they would take on considerable added importance. To explore this possibility, extracellular single cell recordings were recently obtained from the rat nucleus accumbens (NAc), a forebrain limbic structure often postulated to be involved in many of the cognitive and emotional disturbances of schizophrenia [68, 91, 111]. Preliminary studies indicate at least two different effects of LSD in this structure: (1) a predominant inhibitory effect as previously demonstrated in other forebrain structures [5,6], and (2) a potentiating effect on the excitatory (modulatory?) action of 5-HT which was evident on a small subset of neurons, interestingly, this potentiating effect of LSD on 5-HT-induced rate increases occurred on a spontaneously active neuron, but not when glutamic acid was iontophoresed to activate a quiescent NAc (Fig. 4). This is in contrast to the facial motor nucleus where LSD potentiated the ability of 5-HT to decrease the amount of glutamic acid

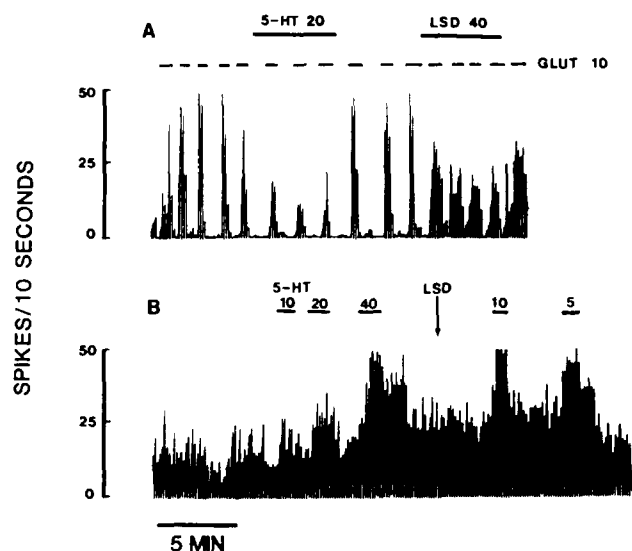


FIG 4 Effects of microiontophoretically administered 5-HT (0.3 M) and LSD (0.01 M) on the activity of two nucleus accumbens (NAc) neurons. A Both 5-HT and LSD inhibited the ability of glutamate (GLUT, 0.01 M) to activate the firing of this quiescent NAc neuron. B 5-HT increased the activity of this spontaneously active NAc neuron in a current dependent manner. Intravenous LSD (0.02 mg/kg at arrow) exerted no effect itself but apparently potentiated the ability of low 5-HT currents to increase firing. Numbers represent iontophoretic current in nanoamperes and lines represent duration of iontophoretic application.

necessary to activate quiescent cells. Perhaps in the NAc, the ability of 5-HT to increase the activity of some neurons reflects an endogenous modulatory facilitation of 5-HT on glutamic acid terminals [2]. However, this is speculation based only on preliminary evidence ($n=3$ NAc neurons). It should also be noted that intravenous administration of the 5-HT antagonist pizotifen, but not the DA antagonist haloperidol, blocked this rate-enhancing effect of 5-HT in the NAc. Moreover, the inhibitory effects of LSD and 5-HT on NAc neurons were not blocked by haloperidol but were partially blocked by pizotifen. Thus far, only inhibitory effects of LHM have been observed in the NAc ($n=12$ cells) and these effects were mediated by DA receptors since they were prevented by haloperidol, but not pizotifen. Thus, LHM and LSD differ markedly with respect to their effects in the NAc, suggesting a possible important role for this limbic nucleus in the biobehavioral actions of LSD.

DA Systems

LSD (0.025–0.05 mg/kg) has been shown to decrease the firing rate of some A9 DA neurons in the zona compacta of the substantia nigra [23,100], an effect characteristic of DA agonists which is mediated by DA autoreceptors in the somatodendritic region [3]. However, it should be noted that compared to apomorphine, LSD is very weak in this regard [100]. Moreover, after chronic treatment with DA agonists, LSD increases the firing rate of A9 DA neurons [24], a finding consistent with the hypothesis that LSD acts as a mixed agonist-antagonist at presynaptic DA receptors [31,98].

We have recently conducted a series of experiments designed to compare and contrast the effects of LSD and LHM

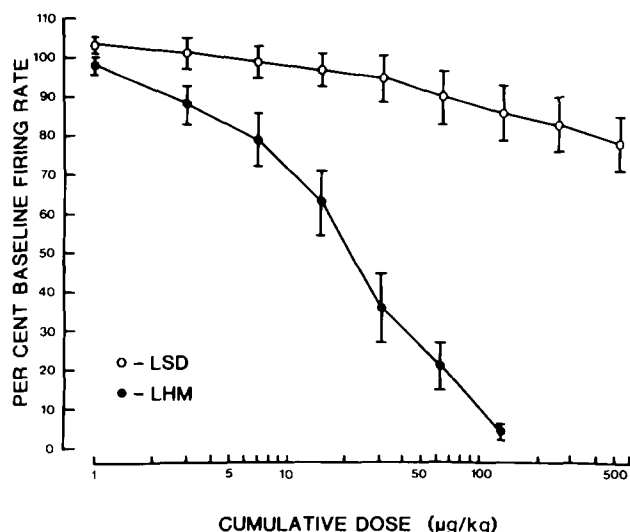


FIG 5 Cumulative log dose response curves of the effects produced by increasing IV doses of LHM or LSD on the firing rates of A10 DA neurons. Data points for LSD represent the mean of 13 rats except for the last data point ($n=8$). Data points for LHM represent the mean of 17 rats except for the last two data points ($n=14$ and 12, respectively). Vertical bars represent standard errors of the mean. Reprinted from [110] with permission (Copyright by Pergamon Press).

on A10 DA neurons in the rat ventral tegmental area [110]. These A10 DA neurons are the primary cells of origin of the mesolimbic and mesocortical DA systems which have been implicated in various cognitive and affective aspects of behavior [88] and, therefore, could possibly be involved in certain cognitive and affective (psychotomimetic) components of the LSD experience.

These experiments demonstrated that LHM potently suppressed the firing rates of A10 DA cells, but failed to consistently alter the firing rates of non-DA neurons in the VTA. The ID_{50} for LHM suppression of A10 DA cells (0.021 mg/kg, see Fig. 5) was similar to that reported for LHM on A9 DA cells [100]. As previously demonstrated on A9 DA cells [100], haloperidol was ineffective in reversing the LHM-induced suppression but was capable of preventing the effect (Fig. 6), suggesting that LHM acted as a noncompetitive or irreversible DA agonist, as was recently demonstrated for another ergot derivative, bromocriptine [12]. This interpretation is supported further by the fact that, following partial suppression of an A10 or A9 DA neuron by LHM, apomorphine was unable to suppress further the firing rate of the cell (Fig. 6). Unlike LSD (see below), LHM did not exert a typical DA antagonist effect because LHM failed to reverse apomorphine's rate-depressant effects on A10 DA cells.

In contrast to LHM, LSD exerted mixed effects on A10 DA cells, partially suppressing the firing of some cells, accelerating the firing of some cells and exerting no effects on others (Fig. 7). Interestingly, our results suggested that A10 DA cells with firing rates above 3.0 Hz were more likely to be suppressed by LSD than A10 DA cells with firing rates below 3.0 Hz. This relationship between the effects of LSD

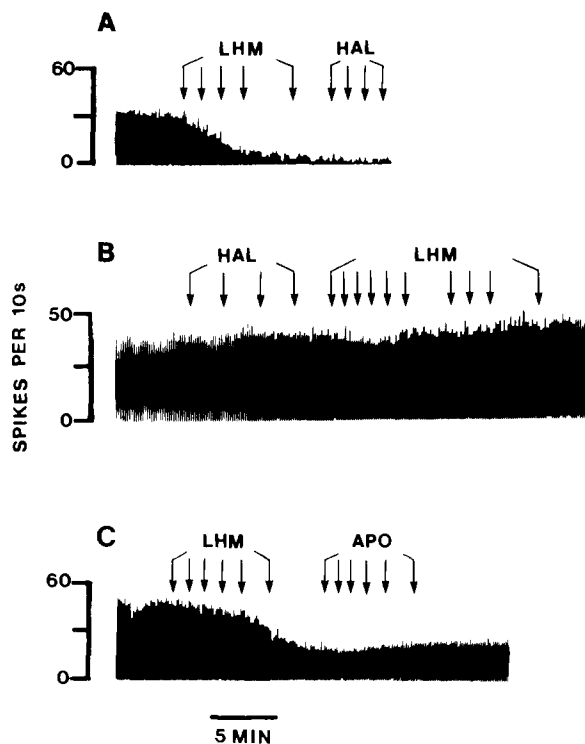


FIG 6 Effects of LHM on the firing rates of A10 DA neurons. A Typical suppression of the firing rate of an A10 DA neuron produced by increasing IV doses of LHM (0.001–0.016 mg/kg, total dose, 0.031 mg/kg) and the inability of haloperidol (HAL) (0.05–0.4 mg/kg IV, total dose, 0.75 mg/kg) to reverse the suppression. B Prevention of the rate-suppressant effects of increasing IV doses of LHM (0.001–0.512 mg/kg, total dose, 1.023 mg/kg) on an A10 DA neuron by pretreatment with HAL (0.005–0.04 mg/kg, total dose, 0.075 mg/kg IV). C Partial suppression of the firing rate of an A10 DA neuron produced by increasing IV doses of LHM (0.001–0.032 mg/kg, total dose, 0.063 mg/kg) and the failure of apomorphine (APO, 0.001–0.032 mg/kg, total dose, 0.063 mg/kg IV) to further suppress the firing rate of the cell. Reprinted from [110] with permission (Copyright by Pergamon Press).

and basal activity is exactly the opposite of that reported for the DA agonists apomorphine, amphetamine, pergolide, and LHM [109]. The potency with which these agonists inhibit A10 DA neurons is indirectly related to basal activity such that agonist-induced rate suppression is more pronounced on slower firing DA neurons [109]. The reasons for the unusual nature of LSD's interactions with individual DA neurons are unknown but these data suggest that the inhibitory effects of LSD on A10 DA neurons are mediated via somewhat different mechanisms than those of more potent DA agonists. Perhaps LSD exerts inhibitory effects only on a particular subset of A10 projection neurons terminating in some specific forebrain area. Further experimentation utilizing site-specific antidromic stimulation techniques will be required to investigate this possibility.

The haloperidol-reversible partial suppression of A10 neuronal activity by LSD suggests that LSD is only a weak DA agonist *in vivo*, a conclusion that is supported by previous biochemical [63] and behavioral [53] studies. As previously demonstrated on A9 DA neurons [24], LSD also exerted what appears to be an antagonist action on A10 DA

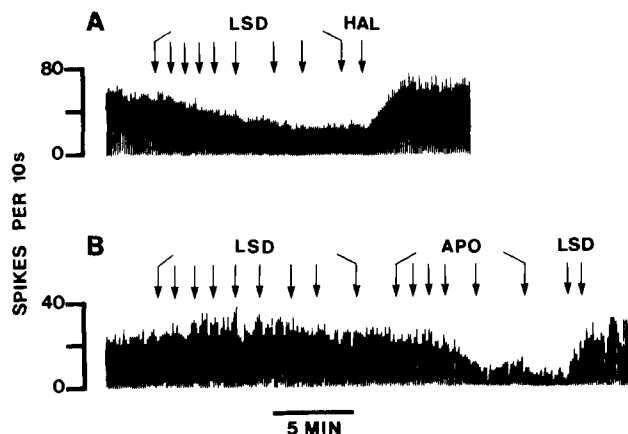


FIG 7 Effects of LSD on the firing rates of A10 DA neurons. A Partial suppression of the firing rate of an A10 DA neuron produced by increasing IV doses of LSD (0.001–0.128 mg/kg, total dose, 0.511 mg/kg IV). B Increases in the firing rate of an A10 DA neuron produced by increasing IV doses of LSD (0.001–0.256 mg/kg, total dose, 0.511 mg/kg), the subsequent partial suppression of the firing rate of the cell by increasing IV doses of apomorphine (APO, 0.001–0.032 mg/kg, total dose, 0.063 mg/kg) and the reversal of APO's effect by LSD (0.05 and 0.1 mg/kg IV). Reprinted from [110] with permission (Copyright by Pergamon Press).

neurons, reversing the rate-depressant effect of apomorphine. This reversal apparently was not due to a 5-HT agonist action of LSD because, unlike the 5-HT agonist 5-MeODMT, LSD was not able to accelerate the activity of LHM-suppressed A10 DA cells. Thus, our results seem to be consistent with many previous reports that LSD is a weak DA agonist which also exerts partial DA antagonist-like actions [23, 24, 63, 98, 100]. DA-antagonist properties of LSD may also be responsible for the increased firing rate of some A10 DA cells seen following LSD administration because DA antagonists typically accelerate the firing of A10 DA cells (Fig. 6B). Additional research is needed to identify the projection areas of those DA neurons which are activated by LSD.

To discern whether these drug-induced alterations in the activity of A10 DA neurons were direct effects on the A10 cells or were possibly mediated transynaptically, experiments using direct microiontophoretic application of LSD and LHM onto A10 DA cells were performed. LHM, like DA, inhibited the activity of A10 DA neurons (Fig. 8A, [108]), an effect that was prevented, but not reversed by the DA antagonist, trifluoperazine. These results indicate that the noncompetitive action of LHM on A10 DA neurons occurs directly on DA autoreceptors which are of the D-2 receptor subtype [112]. Microiontophoretic application of LSD onto A10 DA neurons resulted in both a weak rate suppressant effect and a partial reversal of DA's rate suppressant action (Fig. 8B). Thus, it appears that LSD exerts mixed DA agonist/antagonist actions on DA autoreceptors.

NE Systems

In contrast to its depressant effects on raphe and nigral cells, intravenous LHM, in higher doses (0.025–0.05 mg/kg), causes an increase in the cellular activity of some NE neurons on the locus coeruleus [81], LSD has a similar, but

less pronounced effect [92]. This activation of NE neurons is consistent with reports of α -adrenoceptor antagonist effects of both LHM and LSD and the typical finding that LHM is more potent than LSD in this action (above).

CONCLUSIONS

It is readily obvious that the spectrum of LHM's potent neuropharmacological and biobehavioral actions has played havoc with the major current hypotheses regarding the neuronal mechanisms through which LSD exerts its powerful hallucinogenic properties. Discovering the shortcomings of such hypotheses appears, at least in hindsight, to have been inevitable since it is unlikely that any simple theory of hallucinogenic mechanisms could ever account for the multifaceted components of so striking an experience as that induced by hallucinogens. As cogently argued by Freedman and colleagues [39], the necessary orientation for future research is toward essential component parts (both in temporal and dosage parameters) of the LSD experience and their correlation with biochemical and electrophysiological events in the nervous system. The problem in this respect is the paucity of reliable and replicable pharmacologic parameters in humans from which to deduce such correlations. For this reason, the following discussion will attempt to correlate biochemical and electrophysiological findings with data gathered from various behavioral assays in animals, making the admittedly large assumption that such behaviors are, in fact, reliable predictors or analogues of human behavior.

The original proposal that LSD's hallucinogenic effects were due to a decrease in 5-HT turnover failed to account for many of the key biochemical events occurring in the first sixty minutes of LSD administration [39]. The fact that LHM produces strikingly similar biochemical changes with respect to 5-HT turnover prompted some researchers to dismiss this action of LSD as an "epiphenomenon unrelated to hallucinosis" [74]. We have argued elsewhere [102] that these common effects of LSD and LHM indicate that effects on 5-HT turnover are not alone sufficient for inferring hallucinogenic efficacy. The available evidence linking 5-HT neuronal events to LSD's actions are certainly far too compelling to be dismissed outright. As pointed out above, considerably more research must be conducted on LSD and LHM with respect to membrane and subcellular events involved in 5-HT (and CA) storage and release mechanisms.

The popular hypothesis that hallucinogenic efficacy is related to the ability of such drugs to inhibit the activity of 5-HT neurons [5,6] has also been called into question by the greater potency of LHM than LSD at inhibiting raphe neurons [81]. Yet the fact that LHM is also more potent than LSD on postsynaptic 5-HT receptors (Wang and Aghajanian, unpublished results) is compatible with the presynaptic selectivity hypothesis of hallucinogenic potency. Nevertheless, several other lines of evidence argue against a simple "inhibition-disinhibition" mechanism (see Electrophysiological Studies, above). This is not meant to imply that inhibition of dorsal raphe 5-HT neurons is not involved in hallucinogenic efficacy but rather, to suggest that such an effect is not a sufficient condition for the overall composite characteristic of the psychedelic experience. Given the minute doses of LSD which inhibit raphe neurons and the rapid onset of this event, it seems at least possible that raphe inhibition may be required to initiate other neuronal events which then propagate and sustain hallucinatory-related consequences. However, it is clearly not the case that these

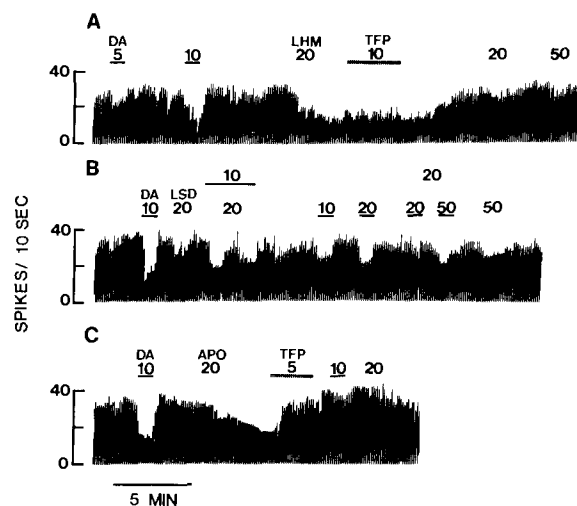


FIG 8 Comparison of the effects of microiontophoretically administered LHM (0.01 M), LSD (0.01 M), DA (0.1 M) and apomorphine (APO, 0.01 M) on A10 DA neurons in the rat. A: DA readily suppressed the activity of this cell and the effect was rapidly reversed upon current termination. In contrast, LHM caused a prolonged suppression of activity which was not reversed by trifluoperazine (TFP, 0.05 M). However, after the cell recovered to basal levels, LHM was no longer capable of suppressing the cell. B: LSD caused a slight suppression of this cell's basal firing and both partially reversed and partially prevented the rate-suppressant effect of DA. C: Like LHM, APO caused a prolonged rate suppression of this cell but unlike LHM, TFP readily reversed the effect of APO. TFP also prevented further rate-suppressant efficacy of both APO and DA. Numbers indicate iontophoretic currents in nanoamperes and lines represent the duration of iontophoretic application.

subsequent events depend upon a potent direct DA agonist action as previously proposed [94] since LHM is considerably more potent than LSD at DA receptors (see above).

In addition to causing scientists to view these previous hypotheses of hallucinosis with a skeptical eye, the discovery of LHM's neurobiological activities has generated the search for new potential sites of specific hallucinogenic actions, the most promising of which are postsynaptic 5-HT receptors. At about the same time that we were obtaining behavioral evidence indicating that the discriminable (subjective) states elicited by LSD and LHM were distinguishable primarily because of the greater specificity of LSD's interaction with postsynaptic 5-HT receptors [102], McCall and Aghajanian [69] discovered that the ability of LSD (and other hallucinogens) to potentiate 5-HT's excitomodulatory action in the facial motor nucleus was not shared by LHM. More recently, Jacobs and co-workers [50,58] have also reached the conclusion that postsynaptic 5-HT receptors may be the most important sites of hallucinogenic activity. Among the important questions now at hand are (1) which postsynaptic 5-HT receptors are likely to be involved in LSD-induced hallucinosis, (2) in what way are they involved, and (3) what other neuronal actions may result from activation of these 5-HT receptors?

Several investigators have postulated the existence of two or more types of 5-HT receptors in the CNS [2,73]. Clearly, one criterion for accepting or rejecting a particular 5-HT receptor as accountable for hallucinatory phenomena is that LHM should not mimic the effects of LSD on that receptor

or, at the very least, LHM should exhibit considerably less potency. A second criterion for acceptance of certain 5-HT receptors as mediators of hallucinosis might be derived from the behavioral studies reviewed above. Noticeable in almost all cases is the fact that 5-HT antagonists attenuate the behavioral effects of LSD in animals. If we generalize this fact to the human experience, one might expect 5-HT antagonists would also attenuate at least some components of the hallucinogenic experience. Unfortunately there are, at present, no published data either to support or reject this possibility. However, if we accept the validity of the behavioral models reviewed herein, then selective antagonism of LSD's effects by 5-HT antagonists would be a second criterion to apply to 5-HT receptor candidacy. Based on these criteria, only two 5-HT receptors thus far recognized would qualify as potential mediators of hallucinogenic action. One such receptor would be those at which 5-HT exerts an excitatory (or excitomodulatory) action since the effects of 5-HT and, presumably, LSD are blocked by 5-HT antagonists. Such receptors have been identified in the facial motor nucleus [69] and, in preliminary experiments, in the NAc (above). The search for such receptors in other brain areas is an important horizon for future research. A second 5-HT receptor which meets the above criteria also appears to be located in the NAc since both 5-HT and LSD inhibit neuronal activity at this site and these effects are partially blocked by the 5-HT antagonist pizotifen. Although LHM also inhibits NAc neurons, its effects are blocked only by DA antagonists. These are intriguing preliminary results worthy of extensive continued investigation.

With respect to the first 5-HT receptor cited above ("excitatory"), it should be noted that other "excitatory" responses to 5-HT have been reported in the cortex and reticular formation. However, LSD appears to be an antagonist at these sites [19,80], thus making reconciliation of these findings with the 5-HT antagonist-induced reduction of LSD's behavioral effects difficult. Perhaps some components of LSD's actions are due to 5-HT receptor antagonism in the CNS which could explain why some behavioral effects of LSD are partially mimicked by some 5-HT blockers [25,59]. Unfortunately, the effects of LHM have not been evaluated on these "excitatory" 5-HT receptors.

The above discussion is not designed to exclude completely those 5-HT receptors which are not blocked by antagonists from a potential role in hallucinatory events. Given the lack of human clinical data, such exclusion is certainly premature. Obviously needed are detailed clinical

studies of a variety of 5-HT antagonists with emphasis on particular aspects of LSD's spectrum of effects, with such information it would then be possible to correlate specific neuronal effects with specific components of the LSD experience. Thus far, the majority of antagonist data acquired from human studies utilized DA blockers which were reported in some cases to reduce the intensity of the LSD reaction [56]. These results are often cited as supporting a DA agonist action of LSD [31, 74, 75]. However, as argued convincingly by Freedman *et al* [39], there is no sufficiently compelling evidence that DA antagonists specifically block LSD effects as opposed to merely causing sedation. Until more detailed, controlled and nonanecdotal clinical findings are forthcoming (which is unlikely given current constraints), we must continue to rely on animal models and, therefore, the criteria suggested above are offered as a working hypothesis on which to base future research.

In conclusion then, it is certainly true that the effects of LSD reported in the literature are multifaceted and divergent, implicating a variety of different but probably interrelated neuronal mechanisms as potentially accountable for the various components of the LSD experience. The discovery of the nonhallucinogenic compound LHM which bears such close structural and pharmacological similarity to LSD provides a powerful tool to the hallucinogen researchers with which to unmask those neuropharmacological mechanisms unique to the hallucinogens. The studies thus far completed continue to emphasize the dominant role of 5-HT neuronal systems but now have led us to explore in greater detail the precise sites at which LSD's interactions with this system are discrepant from those of LHM. Much work is left to be done, not only along the avenues traveled thus far, but also down new paths through unexplored territories. Given the recent growth of our knowledge of neuropeptide systems, a potential area for future research is the possible interplay between hallucinogens, 5-HT systems and specific peptide neuromodulators (see [32a]). Continued endeavors in this and other quests will hopefully shed new light into the unique neurobiological events which unfold to produce the psychedelic experience.

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