DISCRIMINATIVE STIMULUS PROPERTIES OF HALLUCINOGENS: BEHAVIORAL ASSAY OF DRUG ACTION

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I. INTRODUCTION

In this chapter we will review existing literature on the discriminative stimulus properties of several drugs which are often classified as hallucinogens. At the same time we will try to answer several questions about the usefulness of this procedure. For example, can it be used as a specific behavioral assay or screening technique for hallucinogens? Can the mechanism of action of hallucinogenic drugs be effectively studied and, if so, can it tell us anything about the nature of hallucinations?

Hallucinogens, for the present purpose, are those compounds which have in common the ability to induce "psychotomimetic"-like effects in humans. While the prototypic drug in this class is lysergic acid diethylamide (LSD), we will also discuss psilocybin, mescaline, ditran, and phencyclidine (PCP). Although almost any drug in large enough doses can induce hallucinations in man, we have simply restricted the scope of our review to include those drugs not covered in extenso elsewhere in this volume. Partial reviews on this subject have appeared previously (Barry, 1974; Winter, 1974a).

II. METHODOLOGICAL CONSIDERATIONS

Any number of experimental procedures have been used to study the discriminative stimulus properties of hallucinogens. The two most frequently studied are shock escape in either a

T-maze or a three compartment box and choice responding for food or water reinforcement in two lever operant chambers [see Overton (1974) for a complete discussion of methodology]. The lever-pressing situation is somewhat more flexible because different schedules of reinforcement can be used to produce different rates of responding. Since response rate is apparently independent of choice, the effects of drugs on both of these variables can be studied simultaneously and thus provide additional information.

Drug discrimination experiments can be classified into two broad categories, transfer and antagonism, each of which involves a specific purpose. In transfer experiments, rats which have been trained to discriminate some drug from placebo are given various "test" compounds to study the degree of similarity (generalization) between training and test (drug) stimuli. With hallucinogens, transfer experiments are often concerned with the hypothesis that drugs which have similar subjective effects in man will also have similar discriminative stimulus properties in rats. In antagonism experiments, attempts are made to block (or in some cases potentiate) a drug cue with treatments which alter the functional activity of transmitter containing neuronal systems. The aim of these studies, of course, is to delineate the mechanisms which mediate the drug cue and, perhaps, additional related properties (i.e. subjective effects in man).

Obviously, before testing of any kind can be accomplished, the drug discrimination must first be established. Existing operant procedures for training drug discriminations are often laborious and time-consuming (see Colpaert et al., 1976). Typically, rats are first trained to lever press; after responding is "appropriate" to the schedule of reinforcement, drug and placebo injections (discriminative stimuli) are given to establish choice responding (left or right lever pressing). By combining these two phases we have found that acquisition of a drug-placebo discrimination can be facilitated at least for some drugs. Thus, on Day 1 of training, water deprived rats are injected with the drug solvent (usually 0.9% NaCl) and shaped to press one lever (the saline lever); the other lever is removed. The initial schedule of reinforcement on Day 1 is FR 1 (i.e., each barpress results in water reinforcement). This schedule is gradually increased to FR 32 throughout Days 1 and 2. On Day 3 rats are injected with the training drug and placed in the operant chamber with only the other (drug) lever present. Pressing the drug lever results in water reinforcement initially on an FR 1 and as before this schedule is rapidly increased from FR1 to FR 32. On Day 4 drug injections are repeated and training continues on the drug lever (FR32). Training progresses on a double alternation

sequence until all rats have had the opportunity to respond for 4-6 days on each lever (preceded by appropriate injections). Thereafter, rats are given either drug or placebo and placed in the chambers with both levers present. Responding on the lever appropriate for the substance injected is reinforced on an FR 32 schedule of reinforcement. Responding on the inappropriate lever has no programmed consequences. Discrimination training continues until rats' initial choice (i.e., the 32 responses prior to the first reinforcement) is greater than 90% correct. Using this "errorless" training procedure we have found that rats learn various drug (LSD, pentazocine)-solvent discriminations to a level of 90% correct in 10-15 days. Our procedure might produce even more rapid acquisition if incorrect responding were punished (e.g., resulted in a time-out or foot shock).

Once the drug discrimination is established transfer tests and antagonism studies can be initiated. After treating rats with the test drug of interest we place the animals in the operant chambers and allow responding to continue until 32 responses have been emitted on one lever or the other. The rats are then removed from the apparatus without having been reinforced (extinction). Test data should always be gathered in extinction to avoid confounding subsequent results by allowing additional learning to occur.

III. GENERAL CHARACTERISTICS

Before proceeding to the discussion of data from transfer test and antagonism studies we will briefly describe some general characteristics of the discriminative stimuli produced by hallucinogens. It has been demonstrated for PCP and ditran, at least, that acquisition of a drug discrimination is dose related (Jarbe et al., 1975). The larger doses produce the most rapid acquisition as expected. If the dose is too small, acquisition may be protracted or may not occur at all. Once a drug discrimination is well established tests with various doses of the training drug produce orderly variations in response choice. This is true for LSD (Cameron and Appel, 1973; Hirschhorn and Winter, 1971; Greenberg et al., 1975a) and mescaline (Browne et al., 1974; Browne and Ho, 1975b; Hirschhorn and Winter, 1971). Overton (1974) has pointed out that dose-response gradients for drug discriminability are determined largely by the training dose used to establish the discrimination. Therefore, tests with other doses of the training drug are not dose response functions for discriminability, in a pharmacological sense, because this variable should not be influenced by the training dose. Thus, dose response curves represent relative, not absolute, relationships between the test doses and the training dose. We recently found

that the sensitivity to (or discriminability of) submaximal doses of LSD could be altered by a behavioral manipulation (Greenberg et al., 1975a). After completing a dose response study in rats trained to discriminate 80 ug/kg of LSD from saline, we reinforced rats for responding on the LSD lever after 10 ug/kg. This dose originally produced only 30% responding on the LSD lever (in extinction). It was evident that the rats quickly learned this new discrimination; lever choice after 10 ug/kg of LSD reached over 80% after just eight injections of this lower dose. We then returned the rats to the original discrimination (80 ug/kg LSD vs. saline) and re-determined the dose response curve. These data are presented in Fig. 1. We found that the dose response curve was shifted to the left as a result of reinforcing rats at the lower dose of LSD. These data point out the importance of the training dose in determining subsequent dose response relationships. In addition, our results with these extremely low doses of LSD point to the sensitivity and flexibility of the drug discrimination procedure.

Another important variable in behavioral pharmacological experiments is tolerance, defined as the diminution in a (behavioral) response to a drug after repeated administration of that drug. Tolerance to the stimulus properties of hallucinogens has not been extensively studied. A dosage regimen of LSD (acute tolerance) which produces tolerance to the disruptive effects of LSD (Freedman et al., 1964) does not produce tolerance to the LSD stimulus (Cameron and Appel, 1973). Winter (1974a) observed that a mescaline-saline discrimination was not disrupted if LSD was administered after each saline session. In view of the data we just presented (Fig. 1), it may be difficult to demonstrate tolerance to the stimulus properties of a drug. Repeated drug injections may indeed result in a reduced effect (tolerance) but the animals' ability to discriminate may not decrease because they are learning to discriminate smaller doses of the training drug. Additional studies are needed to assess tolerance to drug stimulus properties.

IV. RESULTS

A. Transfer Tests with Hallucinogens

The results of transfer tests with hallucinogens are presented in Tables 1 and 2. LSD can exert control over choice responding under a variety of experimental conditions (Cameron and Appel, 1973; Hirschhorn and Rosecrans, 1974, 1976; Hirschhorn and Winter, 1971, 1975; Schechter and Rosecrans, 1972) at extremely low doses (0.01 mg/kg in rats (Greenberg et al., 1975a). It is typically found that other indole amine hallucinogens such as psilocybin and phenylethylamine hallucinogens such as

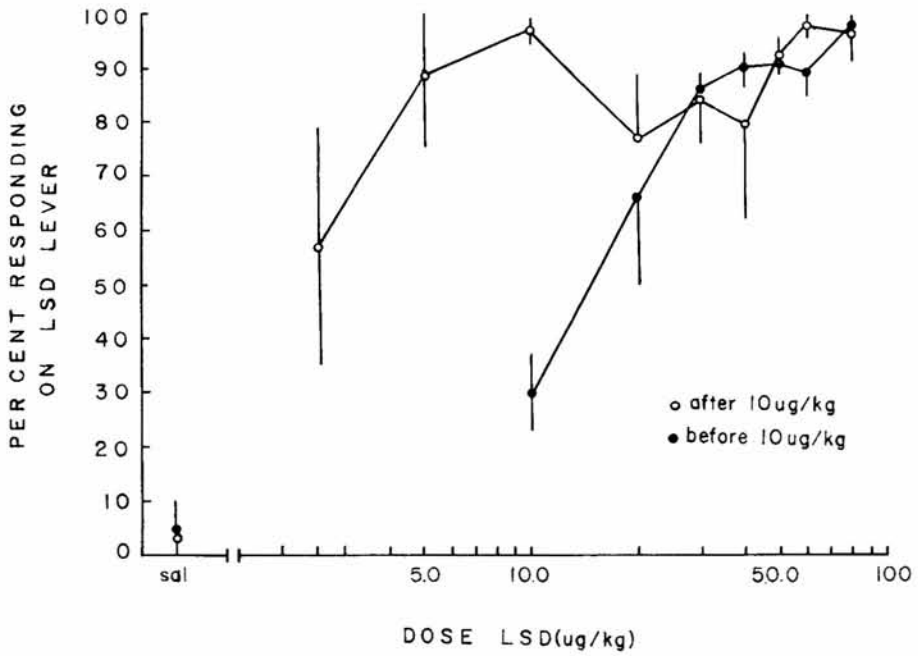

Fig. 1. Per cent of total responding on the LSD lever after various doses of LSD (log scale). Solid circles represent lever choice before the rats were trained to discriminate 10 ug/kg of LSD; open circles represent redetermination of the dose response curve after reinforcing the rats for responding on the LSD lever after 10 ug/kg of LSD. Vertical lines represent ± S. D. All injections were administered 30 min before testing in extinction for lever choice. Each data point is the average of three replications of each dose for 6 animals. (Reproduced with the permission of Psychopharmacology)

Table 1. Drugs which produce discriminative stimuli similar to an hallucinogen

Training	Dose (mg/kg)	Testing	Dose (mg/kg)	Reference
LSD	0.048	Mescaline	22.3,29.7	Schechter & Rosecrans, 1972
	"	Psilocybin	2.5	"
	0.08	Mescaline	8.0	Cameron & Appel, 1973
	"	Scopolamine	4.0	"
	0.10	Cyclazocine	1.0	Hirschhorn & Rosecrans, 1976
Mescaline	10.0	TMPEA	10.0	Winter, 1973
	"	DOM	0.03	Winter, 1975
	"	DOET	0.03	"
	25.0	DMM	50.0	Browne et al., 1975
	"	Mescaline	0.075*	"
Ditran	3.125,6.25	Atropine	25.0	Jarbe et al., 1975
PCP	1.0-2.0	Cyclohexamine	0.75-1.0	"
	2.0-6.0	Ketamine	25.0-35.0	"

*Injected intraventricularly

Table 2. Drugs which do not produce discriminative stimuli similar to an hallucinogen

Training	Dose (mg/kg)	Testing	Dose (mg/kg)	Reference
LSD	0.028	Barbital	20.0-160.0	Hirschhorn & Winter, 1975
	0.048	d-amphetamine	2.0,4.0	Schechter & Rosecrans, 1972
	0.072	Morphine	5.0-20.0	Hirschhorn & Rosecrans, 1974
	0.08	Chlorpromazine	0.5	Cameron & Appel, 1973
	"	d-amphetamine	1.0	"
	0.10	Methadone	1.0-6.0	Hirschhorn & Rosecrans, 1976
	"	Meperidine	5.0-10.0	"
	"	Pentazocine	5.0-20.0	"
	"	Nalorphine	1.0-40.0	"
Ditran	3.125,6.25	PCP	2.0-4.0	Jarbe et al., 1975
	"	Δ^8-THC	5.0	"
Mescaline	10.0	DMPEA	10.0-30.0	Winter, 1974b
	"	d-amphetamine	0.1-1.0	Winter, 1975
	"	Cocaine	3.0-30.0	"
	25.0	NMM	10.0-50.0	Browne et al., 1974
	"	NMM	0.025-0.20*	"
	"	TMPA	25.0	Browne & Ho, 1975a
	"	TMPE	25.0-50.0	"
	"	N-acetylmescaline	50.0	"
PCP	2.0-6.0	Ditran	6.25	Jarbe et al., 1975
	"	Δ^9-THC	5.0	"
	"	Δ^8-THC	10.0	"
	"	Pentobarbital	12.5-18.75	"
	"	Morphine	10.0	"
	"	Chlorpromazine	5.0	"

*Injected intraventricularly

mescaline generalize to the LSD stimulus cue (Cameron and Appel, 1973; Hirschhorn and Winter, 1971; Schechter and Rosecrans, 1972). The dysphorigenic narcotic antagonist cyclazocine partially transfers to LSD but nalorphine, which is pharmacologically and subjectively similar to cyclazocine in man (Haertzen, 1970), does not (Hirschhorn and Rosecrans, 1976). There are reports that the cholinolytic agent, ditran, and the dissociative anesthetic, PCP, are psychotomimetic in man (Hollister, 1964; Ketchum et al., 1973). Thus we gave both of these drugs to rats trained to discriminate 0.08 mg/kg LSD from saline. The results are presented in Table 3.

Table 3. Results of transfer test and antagonism studies in rats (N= 12) trained to discriminate 0.08 mg/kg of LSD from saline.

Treatment (mg/kg)	% Responding on LSD Lever
LSD	94.2
saline	4.3
Ditran (1.0)	40.0
(3.0)	26.1
PCP (1.0-4.0)	10.0
Quipazine (2.5)	81.0
LSD + MTP (0.10)	61.2
+ MTP (0.25)	67.2
+ MTP (0.50)	56.0
+ MTP (1.00)	21.7
LSD + HAL (0.50)	93.6
+ HAL (1.00)	95.4

LSD, saline, ditran, and PCP were injected 15 min prior to testing rats for lever choice in extinction. Methiothepin (MTP) and haloperidol (HAL) were given 1 hr before LSD. Quipazine was given 30 min prior to testing for transfer.

Ditran results in a partial transfer to LSD whereas PCP does not. It is interesting that Cameron and Appel (1973) found that scopolamine partially transfers to LSD. We also tested our rats with quipazine, a putative, direct serotonin receptor agonist (Hong et al., 1969), and observedan almost complete transfer to LSD (Table 3). A large variety of compounds do not transfer to LSD; these are listed in Table 2.

While little research has been done with other indole amine

hallucinogens, it has been determined that psilocybin has discriminable properties of its own (Greenberg et al., 1975b; Harris and Balster, 1971).

Numerous studies have established that mescaline has potent discriminative stimulus properties (Hirschhorn and Winter, 1971; Browne et al., 1974; Browne and Ho, 1975 a,b,; Winter, 1973, 1974b, 1975). Much of this research has been devoted to determining if the discriminable cue produced by mescaline is due to mescaline itself or to a structural isomer or metabolite of the parent compound. The stimulus properties of mescaline (3,4,5-trimethoxyphenylethylamine) have been compared to those of its non-hallucinogenic congeners 2,3,4-trimethoxyphenylethylamine (TMPEA) and 3,4-dimethoxyphenyl-ethylamine (DMPEA). TMPEA was shown to produce a discriminable cue and to mimic mescaline (Winter, 1973). However, DMPEA could neither control differential behavior nor mimic the mescaline cue (Winter, 1974b).

Studies with various metabolites of mescaline have determined that the stimulus properties of mescaline reside in the parent compound. Browne et al., (1974) compared N-methylated derivatives of mescaline to mescaline. They found that N-methyl-mescaline (NMM) did not mimic mescaline whereas N,N-dimethyl-mescaline (DMM) did. Since the doses of DMM required to mimic mescaline were twice as large as the dose of mescaline used for training, the authors concluded that an N-methylated metabolite of mescaline probably does not produce the discriminable cue. Additional studies from the same laboratory (Browne and Ho, 1975a) have more clearly established that the mescaline cue is not mediated by a metabolite. This was accomplished by administering various deaminated and N-acetylated mescaline metabolites to rats discriminating mescaline from saline as well as by inhibiting the enzymes involved in the deamination pathway. The results indicated that the metabolites 3,4,5-trimethoxyphenylethanol (TMPE) 3,4,5-trimethoxyphenylacetaldehyde (TMPA), and N-acetylmescaline did not mimic mescaline. Inhibition of either aldehyde dehydrogenase or monoamine oxidase potentiated the mescaline cue (Browne and Ho, 1975a).

In a recent study, Winter (1976) demonstrated that the ring substituted amphetamines 2,5-dimethoxy-4-methylamphetamine (DOM) and 2,5-dimethoxy-4-ethylamphetamine (DOET) mimic mescaline whereas d-amphetamine and cocaine do not. While DOM is hallucinogenic in man, DOET is not (Snyder et al., 1968, 1974).

Ditran and PCP are discriminable from saline and from each other (Jarbe et al., 1975). Transfer tests have established that the anticholingeric atropine transfers to ditran whereas PCP and

Table 4. Drugs which antagonize the discriminative stimuli of hallucinogens

Training	Dose (mg/kg)	Antagonist	Dose (mg/kg)	Reference
Mescaline	15.0	Cinanserin	15.0	Browne & Ho, 1975b
	"	Methysergide	5.0	"
	"	Cyproheptadine	5.0	"
Ditran	1.6	Tacrine	5.0	Jarbe et al., 1975
	"	Physostigmine	0.5-1.0	"

Table 5. Drugs which do not antagonize the discriminative stimuli of hallucinogens

Training	Dose (mg/kg)	Testing	Dose (mg/kg)	Reference
LSD	0.072	Methysergide	3.0-10.0	Hirschhorn & Rosecrans, 1972
	"	Cyproheptadine	3.0	"
	"	Atropine	0.5-2.0	"
	"	Naloxone	0.1-0.4	"
	0.08	Chlorpromazine	0.5	Cameron & Appel, 1973
Mescaline	15.0	Xylamidine	1.0	Browne & Ho, 1975b
	"	Atropine	not reported	"
	"	Phentolamine	"	"
	"	Propranolol	"	"
	"	Amphetamine	"	"
	"	Strychnine	"	"
	"	Pimozide	"	"
	"	Picrotoxin	"	"
Ditran	1.6	Yohimbine	5.0	Jarbe et al., 1975
	"	Neostigmine	0.4	"
PCP	2.0	PCPA	310.0	"
	2.0-6.0	TBZ + IMI*	10+2.5,20+5.0	"

*Tetrabenazine + Imiprimine

Δ^8THC did not (Table 1B). A variety of compounds were also tested for transfer to PCP. Only the structurally related agents ketamine and cyclohexamine mimicked PCP (Jarbe et al., 1975).

B. Antagonism Studies with Hallucinogens

Only limited data are available on the ability of various compounds to attenuate the stimulus properties of hallucinogens. These results are summarized in Tables 4 and 5. Attempts to block the LSD cue with the putative serotonin receptor antagonists cyproheptadine and methysergide, with the anticholinergic atropine, and with the narcotic antagonist naloxone were unsuccessful (Hirschhorn and Rosecrans, 1974). However, we have recently observed a dose related blockade of the LSD stimulus cue following pretreatment with the neuroleptic methiothepin. These data are also included in Table 3. Interestingly, methiothepin displaces LSD from the recently identified LSD receptor (Lovell and Freedman, 1976). We were unable to block LSD with the dopamine receptor antagonist haloperidol.

The stimulus properties of mescaline can be blocked by cinanserin, methysergide, and cyproheptadine; the peripheral serotonin antagonist xylamidine tosylate is without effect (Browne and Ho, 1975b). Depletion of brain serotonin with the tryptophan hydroxylase inhibitor p-chlorophenylalanine (PCPA) potentiates the stimulus properties of submaximal doses of both LSD (Cameron and Appel, 1973) and mescaline (Browne and Ho, 1975b).

Antagonism studies have also been carried out with ditran and PCP. The stimulus cue produced by ditran was blocked by the anticholinesterase agents tacrine and physostigmine, but was unaffected by yohimbine and neostigmine (Jarbe et al., 1975). The discriminative stimulus produced by PCP was neither disrupted by PCPA pretreatment nor blocked by a combination of tetrabenazine and imiprimine which effectively blocks other effects of PCP in rats (Tonge and Leonard, 1972).

V. DISCUSSION

A. Transfer Tests

As mentioned earlier, transfer tests have been carried out in an effort to determine if drugs which have similar subjective effects in man have similar stimulus properties in rats. It was hoped that whatever property causes a drug to be hallucinogenic in man would be the property which makes the same drug discriminable in rats so that the discriminable properties in rats could serve as a useful animal model for predicting and analyzing

hallucinogens. Apparently, this has not proven to be the case. For example, TMPEA and DOET, which are not hallucinogenic, transfer to mescaline; cyclazocine, which is subjectively differentiable from LSD in humans, partially transfers to LSD in rats but nalorphine and pentazocine do not; quipazine transfers to LSD but, unfortunately, little is known about its subjective effects in man. Indeed, it seems clear that the drugs presently discussed as hallucinogens are even quite different in terms of their discriminative stimulus properties.

While the behavioral procedure we have been considering may not be an accurate assay of the ability of compounds to induce hallucinations, it does have the capability to detect very subtle features of drugs (structural, resonance form) upon which discriminable similarity is apparently based. For example, only the structurally related drugs ketamine and cyclohexamine transfer to PCP. Thus, the drug discrimination procedure could be used to screen compounds for similarity specifically to LSD, specifically to mescaline etc. Whatever structural variables make such drugs discriminably similar in rats may be necessary to cause similar subjective effects in man but they are not sufficient. We must realize that the task of devising a behavioral assay which is specific for hallucinogens is complicated from the outset by our lack of knowledge of what hallucinations are and the variability inherent in subjective reports of drug effects in man. Indeed, while LSD, mescaline, psilocybin, ditran, and PCP are all reported to induce hallucinations, an LSD hallucination must certainly be different from a ditran or a PCP hallucination. Thus, the usefulness of this procedure is not diminished because it is not a specific assay for hallucinogens. No procedure is. It is, however, one of few behavioral procedures which is sensitive and specific enough to distinguish differences among the various "hallucinogens". Hopefully, subsequent transfer studies will concentrate on structure-activity relationships to determine those features of drugs which make them discriminably similar.

B. Antagonism Studies

The purpose of antagonism studies has been to delineate the mechanism(s) of drug discriminative cues. For some time now the actions of LSD have been attributed to its direct interaction with the central serotonergic neuronal system (Aghajanian, 1972). The results of an interesting transfer experiment suggest that a postsynaptic serotonin receptor is involved. Hirschhorn et al., (1975) trained rats to discriminate midbrain raphe stimulation from non-stimulation. When injected with LSD their rats responded (lever choice) as if they had been stimulated (Hirschhorn et al., 1975). The quipazine transfer to LSD which we observed

(Table 2) also suggests a serotonergic involvement in the LSD cue. It is not clear to us why the LSD cue was not blocked by the serotonin antagonists cyproheptadine and methysergide (Hirschhorn and Rosecrans, 1974). We have found that these agents do in fact block LSD (unpublished observations). Preliminary evidence from our laboratory suggests, furthermore, that it might be more accurate to attribute the mediation of the stimulus properties of LSD to an LSD (rather than a serotonin) receptor. Methiothepin blocks both the LSD stimulus cue and the recently identified d-LSD receptor (Lovell and Freedman, 1976). Methiothepin and haloperidol are approximately equipotent as dopamine receptor antagonists but at doses equimolar to those of methiothepin, haloperidol does not block the LSD cue.

By virtue of the ability of cinanserin, methysergide, and cyproheptadine to block the mescaline cue,it has been concluded that mescaline exerts its cue by stimulating serotonin receptors (Browne and Ho, 1975b). A central locus for the mescaline stimulus was indicated with the demonstration that intraventricularly administered mescaline transfers in a dose related manner to systemically injected mescaline (Browne et al., 1974).

The stimulus properties of ditran are apparently related to the anticholinergic properties of this compound. The anticholinesterase agents tacrine and physostigmine reverse the ditran cue. Since the peripherally acting neostigmine did not block ditran, a central locus of action is also inferred for the stimulus properties of this drug (Jarbe et al., 1975). Little is known about the mechanisms underlying the PCP stimulus cue. The lack of effect of PCPA on the PCP cue is not sufficient to rule out a role for serotonin because PCP may act directly and independently of an intact serotonin system.

Existing data from antagonism studies indicates that the various hallucinogens may also have different mechanisms of action. There is too little data, however, to draw any conclusions. Interpretation of antagonism studies are further complicated by the lack of knowledge of how and where in the brain many of the drugs typically used as antagonists act. Nevertheless, this procedure is ideally suited to study drug mechanisms of action because of its sensitivity and specificity.

VI. CONCLUSIONS

Drugs capable of inducing hallucinations in man can serve as discriminative stimuli in rats. While drugs which are subjectively similar in man will almost certainly have similar discriminative properties in rats, it does not follow that drugs with similar stim-

ulus properties in rats will be subjectively similar in man. Thus, the hallucinogenic liability of a drug cannot be accurately predicted from transfer tests. Antagonism studies appear to offer some very interesting results but the hallucinogens have not yet been studied extensively enough to be able to accurately assess its usefulness in studying drug mechanisms of action. Obviously, tests with other hallucinogens such as dimethyltryptamine or bufotenine are needed.

VII. ACKNOWLEDGEMENTS

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