Drug-Induced Discrimination: A Description of the Paradigm and a Review of its Specific Application to the Study of Hallucinogenic Agents

Richard A. Glennon, John A. Rosecrans, and Richard Young

Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia 23298

I. INTRODUCTION

In the drug discrimination paradigm, animals are trained to emit a particular response under a certain set of conditions, and a different response under a second set of conditions. For example, an animal can be trained to press one lever in a two-lever operant situation when administered Drug A and to press the opposite lever when administered Drug B. Animals trained to differentiate the effects of two drugs, i.e., animals trained to discriminate Drug A when paired with Drug B, essentially serve as the basis for this behavioral procedure. In a simple case, animals might be trained to discriminate Drug A when paired with saline (as Drug B); in more complex cases, animals can be trained to discriminate between two drugs, between two doses of the same drug, or between two drugs and saline. The ability of a drug to assume

discriminative control of behavior appears to be contingent upon its being able to produce a centrally mediated effect. Furthermore, whereas animals develop behavioral tolerance to the disruptive effects of a training drug, tolerance to the cueing effect or stimulus properties of the drug is not evident. If the latter were not true, a drug would not be able to exert discriminative control of behavior and could not serve as a training drug.

The drug discrimination paradigm can be a powerful tool for medicinal chemistry. Animals trained to discriminate a particular training drug from saline can be administered a series of challenge drugs. Such agents, when administered in a careful dose-related manner, may produce one of several consequences including, at some particular dose, stimulus generalization. Stimulus generalization to a challenge drug is evidence for similarity of effect. Thus, the drug discrimination paradigm may be used to qualitatively and quantitatively compare a series of agents to a particular training drug. Studies of this sort also generate information which can be used to formulate *in vivo* structure–activity relationships (SAR). Mechanism of action can be explored by pretreatment of the animals with various neurotransmitter antagonists in order to determine if stimulus effects can be attenuated. Generalization studies involving neurotransmitter agonists and various neuropharmacological and neurochemical manipulations can also provide valuable information. Although the exact nature of the stimulus cue is not yet fully understood, the drug discrimination paradigm, being a stable, specific and very sensitive measure of dose-related drug effects, provides a rather unique pharma-

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Richard A. Glennon, *after receiving his B.S. degree in Pharmacy and M.S. degree in Medicinal Chemistry from Northeastern University, he was employed as a research chemist at Warner-Lambert Research Institute. He later earned his doctorate in Medicinal Chemistry (1973) from the State University of New York at Buffalo, and was then awarded an Alcohol, Drug Abuse, Mental Health Administration fellowship to pursue postdoctoral training in psychopharmacology in the Department of Pharmacology, School of Medicine, SUNY. He joined the faculty of MCV/VCU in 1975 and is currently Associate Professor of Pharmaceutical Chemistry. In June 1982, Dr. Glennon presented a paper at the International Drug Discrimination Symposium in Belgium on the application of the drug discrimination paradigm to studying hallucinogenic agents; this manuscript is a direct outgrowth, and an extention, of that paper.*

John A. Rosecrans *was awarded a Ph.D. degree in Pharmaceutical Science (Pharmacology) from the University of Rhode Island in 1963. His research interests were in the area of CNS pharmacology and pursued further training in the Department of Pharmacology, at the University of Michigan and in the Department of Psychiatry at Yale University. In 1968, Dr. Rosecrans took a post as Assistant Professor of Pharmacology at the Medical College of Virginia and has since become Full Professor at the same school, which is now Virginia Commonwealth University. Dr. Rosecrans' main research interest involves studying CNS sites and mechanisms of psychotropic drugs and has especially developed the drug discrimination paradigm for this purpose.*

Richard Young *received his B.S. degree from the University of Cincinnati. He received his M.S. and Ph.D. degrees in biopsychology from Virginia Commonwealth University, and is currently a postdoctoral fellow in the Department of Pharmaceutical Chemistry, Medical College of Virginia, VCU.*

cological drug "detection" procedure whereby the actions of centrally active agents can be evaluated.

The discussion that follows is intended to serve as an introduction to the drug discrimination technique. This discussion, while not exhaustive, includes both theoretical and practical considerations necessary for a general understanding of the method. Finally, as an example of the application of drug discrimination, the literature is reviewed with regard to the use of this method to study hallucinogenic agents.

II. THE DRUG DISCRIMINATION PARADIGM

A. Operant Learning Considerations

In general, a stimulus is anything an organism can detect; stimuli may be physical or biological in nature. How can one tell that an organism detects a stimulus? One way to answer this question is to determine whether the stimulus can gain control over behavior. If it can be demonstrated that an organism's behavior is consistently different in the presence of a stimulus than in its absence, it is reasonable to assume that the organism detects the stimulus. Thus, a stimulus may be defined, operationally, in terms of its ability to control behavior. It is within this framework that the discriminative stimulus properties of drugs has flourished.

The central concept of operant learning is that when a response is followed by positive (or reinforcing) consequences, there will be an increase in the probability that this response will occur again under similar circumstances. For example, a typical operant experiment might involve a rat, that is food deprived (the animal's weight is reduced to ca. 75–80% of its expected free-feeding body weight by partial food deprivation) and placed in an apparatus (i.e., operant chamber, or Skinner box) designed to deliver reinforcement (e.g., sweetened milk, or food pellet) to the rat every time a switch mounted beneath a lever is closed. When every response is followed by reinforcement, the organism is said to be on a continuous reinforcement schedule (CRF) or fixed ratio one (FR-1) schedule of reinforcement. As a consequence, the total amount of reinforcement delivered on an FR-1 schedule could become quite high, and might result in decreased responding over time because of satiation. However, it is unnecessary to reinforce every response in order to maintain responding. That is, reinforcement can be programmed to occur on intermittent schedules in which only some responses are reinforced (schedule-controlled responding). In the operant laboratory, the schedule of reinforcement determines which responses are reinforced. We shall discuss two basic intermittent schedules of reinforcement: fixed ratio (FR), and variable interval (VI).

On variable-interval (random-interval) schedules, reinforcement is contingent upon the passage of time and upon a single response. In other

words, the time between reinforcements on VI schedules varies from one reinforcement to the next. The value of the VI schedule is the average time between reinforcements. For example, a variable interval 15-s (VI-15) schedule might make the first reinforcement available after 5 s, the next after 1 min, the next after 45 s, and so on. Although it is possible to obtain reinforcement for each response on a VI schedule by waiting for the inter-reinforcement interval to elapse, there is no way for the animal to predict the length of a particular inter-reinforcement interval.

On a fixed-ratio schedule, reinforcement depends upon the completion of a certain number of responses; time is irrelevant. For example, if the value of the ratio is 32 (FR-32), every 32nd response is reinforced. If the organism responds rapidly, reinforcements may be seconds apart, and if the organism responds slowly, reinforcements may be many minutes apart. The passage of time does not make reinforcement any more likely. Each type of schedule has its own advantages and disadvantages.

As a research instrument, schedule-controlled responding can be extremely valuable. The major advantage of using reinforcement schedules is that they produce very reliable patterns of behavior. The rate and/or pattern of responding on a particular schedule can function as a stable baseline against which the effects of various manipulations can be assessed. In particular, research concerned with the interaction(s) between schedules of reinforcement and various drugs has become quite popular. One can administer drugs to animals, trained on one or another reinforcement schedule, and look for changes in responding. The interested reader should consult Mackintosh,[1] Reynolds,[2] and Seiden and Dykstra[3] for more complex discussions concerning operant procedures and the interactions between schedules of reinforcement and drugs.

B. Discriminative Stimulus Properties of Drugs

1. Methodology

Operant behavior is controlled not only by its consequences, but also by stimuli and events in the environment (external and/or internal) which precede or accompany the behavior. Animals learn that a particular response produces a particular consequence, and that the consequence is available under particular environmental conditions. The operant chamber is particularly well-suited for discrimination tasks, that is, those tasks in which an organism must choose between two (usually) or more levers in order to obtain reinforcement.

The most frequently used discrimination involves a drug versus vehicle (saline) procedure. As an example, rats can be trained to respond on one of the two levers for food, under one drug state (produced by a particular dose of a training drug), while on different days, the same rats are trained to respond on the opposite lever in the nondrug (vehicle/saline) state (Fig. 1). What is controlling the rat's behavior in this

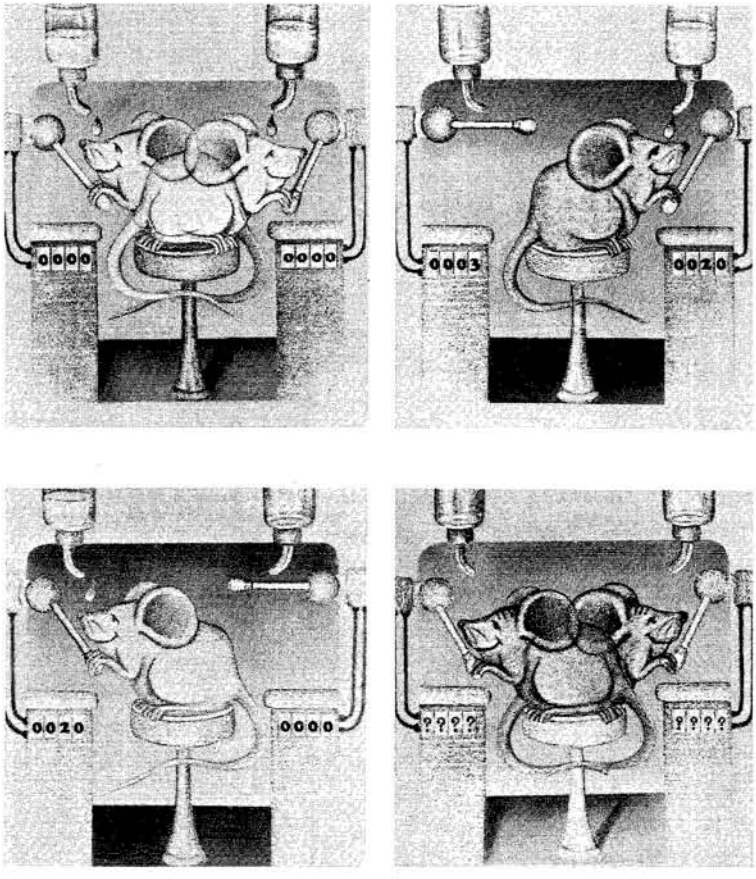


Figure 1. The drug discrimination paradigm. Animals are first trained to press lever for food (milk) reinforcement (upper left panel); animals are then trained to press one lever when administered Drug A (upper right), and the opposite lever when administered Drug B or saline (lower left). During extinction sessions (i.e., in the absence of reinforcement), animals are administered a challenge drug (lower right).

situation? Certainly, that the rat responds on a lever at all is the result of the relation between lever responses and reinforcement. However, that the rat responds on a particular lever under the drug state, and responds on the opposite lever under the nondrug state, must be the result of the relation between the drug state and reinforcement, and the nondrug state and reinforcement, respectively.

To assess the degree of stimulus control in the two-lever choice procedure, occasional periods (at the beginning of the training session) of nonreinforced responding (extinction sessions) are used. The rationale behind the use of these extinction sessions is that the learning of the treatment conditions should be evaluated independently of the reinforcer. For example, Figure 2 shows the acquisition of a pentobarbital

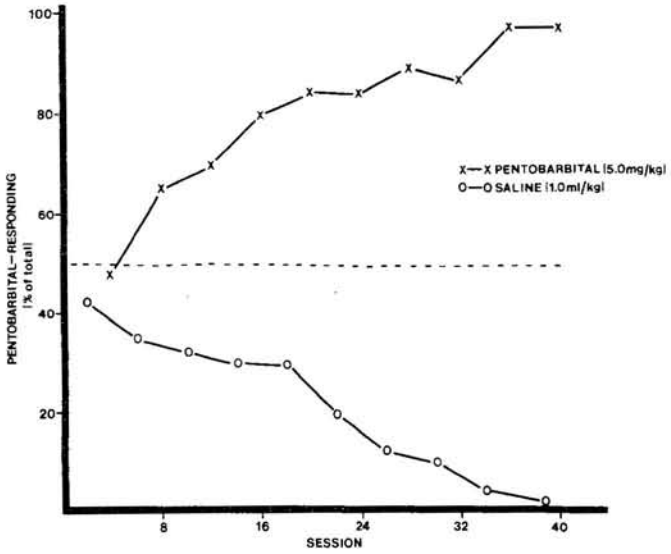


Figure 2. Learning curve for a pentobarbital vs saline discrimination.

versus saline discrimination. The percentage of responses on the pentobarbital-designated lever after pentobarbital or saline administration are shown as a function of training sessions. As can be seen, the administration of pentobarbital or saline during initial training sessions results in the animals dividing their responses equally (ca. 50% drug-lever responding) between the two levers. However, as training sessions progress the animals gradually learn to respond on the drug-designated lever when given drug, and on the saline-designated lever when given saline. Finally, if discriminiation learning occurs, then a high percentage (>80%) of responses will be performed on the drug lever when the animals are given drug. Conversely, a low percentage (<20%) of responses will be made on the drug-designated lever when saline is administered.

Table I lists drugs from several different pharmacological classes which have been shown to act as stimulus cues, i.e., to exert stimulus control over behavior. In most of these studies either the FR or the VI schedule of reinforcement has been employed to establish the discrimination. Once a drug discrimination has been established, classical pharmacological procedures, such as tests of other doses of the training drug (dose-response) and time-course effect can be evaluated. The interested reader should consult Lal,[21] Ho, Richards, and Chute,[22] and Çolpaert and Rosecrans[23] for more extensive discussions concerning the stimulus properties of these agents.

2. Nature of the Cue

The exact nature of the discriminative stimulus (i.e., of the discriminative stimulus cue) is not fully understood, but is generally thought to

Table I
Examples of Studies Demonstrating Discriminative Stimulus Control between Drug and Nondrug Conditions

Agent	Reference
Ethanol	Kubena and Barry[4] Schechter[5]
Amphetamine	Harris and Balster[6]
Apomorphine	Colpaert, et al.[7]
Chlordiazepoxide	Colpaert, et al.[8]
Cocaine	Jarbe[9]
Cyclazocine	Teal and Holtzman[10]
Desipramine	Shearman et al.[11]
DOM	Young et al.[12]
LSD	Hirschhorn and Winter[13]
Morphine	Hirschhorn and Rosecrans[14]
Nicotine	Meltzer et al.[15]
5-OMe DMT	Glennon et al.[16]
Pentazocine	Kuhn et al.[17]
Pentobarbital	Herling et al.[18]
Phencyclidine	Shannon[19]
Tetrahydrocannabinol (Δ^9)	Jarbe et al.[20]

arise from the central effects of a drug. Several studies have been designed in order to evaluate the relative contributions of peripheral versus central factors in a drug's ability to serve as a discriminative stimulus. Rosecrans and Chance,[24] for example, trained rats to discriminate the effects of nicotine from saline. The stimulus control exerted by nicotine was antagonized by mecamylamine, a ganglionic blocking agent that penetrates the blood–brain barrier, but was unchanged by hexamethonium, a quaternary ammonium ganglionic blocker that does not readily enter into the brain. In other studies, Overton[25] has found that, in contrast to atropine, stimulus control could not be demonstrated with atropine methyl nitrate (which does not readily enter the brain) over the course of 50 training sessions. Jones, Hill, and Harris[26] have trained animals to discriminate (+)-amphetamine from saline. In a generalization test, the administration of (±)-parahydroxyamphetamine, which has the peripheral but not the central effects of amphetamine, failed to produce (+)-amphetamine-like responding. Finally, Valentino et al.[27] have trained pigeons to discriminate the effects of morphine from saline; the stimulus control exerted by morphine was antagonized by naltrexone, a narcotic antagonist that crosses the blood–brain barrier, but was undiminished by quaternary naltrexone (at doses 300 times greater than the effective antagonist dose of naltrexone) which enters the brain very slowly following peripheral administration.

From these studies, it might be assumed that the ability of a drug to serve as a discriminative stimulus is the result of an alteration of CNS function, although the exact nature of the change(s), is not known with certainty. However, this is not to imply that all CNS-active drugs will

readily serve as discriminative stimuli. Overton,[28] and Harris and Balster,[29] for example, have reported that their attempts to obtain discriminative stimulus control with chlorpromazine and with imipramine were unsuccessful. In addition, it should not be assumed that all peripherally acting agents are incapable of serving as discriminative stimuli. On the contrary, Colpaert et al.[30] have found that isopropamide, a peripherally acting anticholinergic agent can serve as a discriminative stimulus in rats. What the available data do seem to indicate is that, in general, CNS-active drugs are more efficient as discriminative stimuli than agents which are only active peripherally.

3. *Pharmacological Properties of Drug Stimuli*

As might be suspected, the discriminative stimulus properties of psychoactive drugs are analogous to most of their other CNS pharmacological properties. Thus, drug stimuli are both dose and time dependent. The discriminative stimulus properties of nicotine have been extensively studied and can be used to demonstrate these relationships. In one of the first studies conducted with nicotine, three groups of rats were each trained to discriminate a different subcutaneous dose of this agent from saline (i.e., 0.1, 0.2, and 0.4 mg/kg vs. 1.0 mL/kg of saline). It was clearly demonstrated that the rate of discriminative stimulus learning was dependent upon the training dose (Fig. 3). Furthermore, the sensitivity and duration of the discriminative stimuli were directly related to training dose. Thus, the 0.1 mg/kg training dose group was most sensitive to the effects of nicotine, while the duration of action was

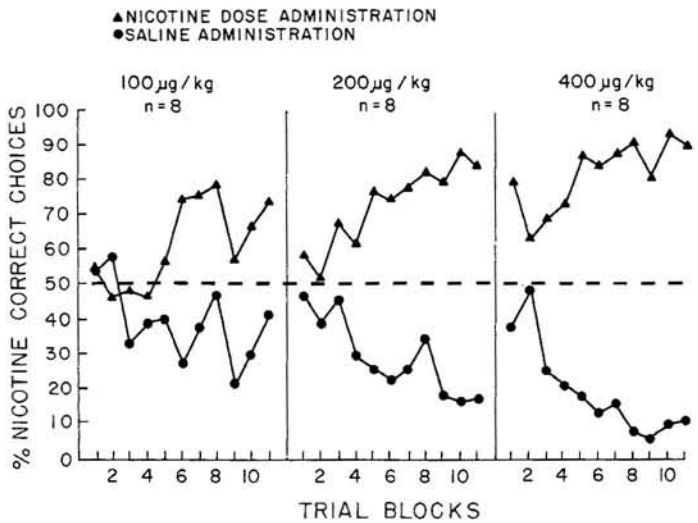


Figure 3. Examples of learning curves employing three groups of rats being trained to discriminate successively higher doses of nicotine from saline.

longer in the 0.4 mg/kg group. Additional work has also demonstrated that these dose and time relationships are directly related to the level of nicotine as measured at the time of behavioral evaluation. Therefore, the drug discrimination paradigm appears to meet the requirements of a pharmacological model for assessing the effects of CNS-active agents. It should be emphasized, however, that because sensitivity and duration of effect are related to a particular training dose of the training-drug, dose-response curves (and ED_{50} values) represent relative, not absolute, relationships for challenge drugs as well as for training drugs. The reader is referred to Overton[31] for a more detailed discussion of this phenomenon.

4. Training-dose manipulation

The sensitivity and flexibility of the drug discrimination procedure are probably best illustrated in studies which manipulate the training dose of the training drug. In particular, these studies suggest that performance on a relatively difficult drug discrimination, for example, that between saline and a very low dose of a CNS-active agent, may benefit from prior training on an easier version of the same discrimination (i.e., saline vs. a "moderate" dose of that same drug). The first study of this type was performed by Greenberg and co-workers[32] who initially trained rats to an LSD (0.08 mg/kg) vs. saline discrimination. These same animals were then reinforced ("retrained," "faded") for responding on the LSD lever at a LSD dose of 0.01 mg/kg. In spite of the fact that the lower dose originally produced only 30% drug-lever responding, the rats quickly learned the "new" discrimination (i.e., 80% drug-lever responding after 0.01 mg/kg of LSD). Since Greenberg's study, Silverman and Ho[33] have examined the effects of retraining in DOM-trained rats and Overton[34] has published a report concerning this procedure using a variety of agents from different drug classes. More recently, White and Appel[35] have examined the effects of LSD training dose manipulation by retraining different groups of animals (from an intermediate LSD-training dose) to a very low LSD dose and to a very high LSD dose. They found that as the training dose of LSD declined, the slope of the LSD dose-response curve became less steep. These data indicate that the training dose of a drug is a very important factor in determining the shape of dose-response curves.

C. Approaches to Studying the Effects of CNS-Active Agents

Because research on human subjects with certain types of CNS-active agents is sometimes limited, the development of a useful animal learning procedure would seem to be a helpful prerequisite to investigations of structure–activity relationships of compounds and to investigations of the interactions between these agents and various neurotransmitter

systems. The drug discrimination paradigm, at this point in time, appears to be one of the most sensitive and rigorous behavioral paradigms that has been developed to study the *in vivo* effects of CNS-active agents. Within the drug discrimination paradigm two general strategies, drug generalization (stimulus transfer or substitution) and drug antagonism, can be employed to study these agents.

1. Generalization Studies

After subjects have been reinforced in the presence of one drug stimulus, they may respond to other drug stimuli that are more or less similar to those present during discrimination training. The occurrence of such responses defines the empirical phenomenon of response generalization (hereafter referred to as stimulus generalization).

The drug generalization approach has been utilized by many investigators to determine whether a drug-induced stimulus will substitute for other drugs of a specific class. The rationale of this approach is that an animal trained to discriminate a dose of a particular CNS-active agent will display stimulus generalization only to agents having a similar effect (though not necessarily an identical mechanism of action). We suggest that animals respond to challenge drugs in a generalization test to the extent that those novel compounds contain pharmacological components which overlap with those produced by a specific dose of the training-drug stimulus. Thus, it may be proposed that the possibility of a drug-appropriate response occurring to a novel test compound (or challenge drug) is some function of the proportion of pharmacological effects in the test set, which because they formed part of the set of pharmacological effects present during training, are associated with reinforcement during discrimination training.

As an example of a generalization test, Glennon and co-workers[36] have trained rats to discriminate the effects of racemic DOM (1.0 mg/kg) from saline in a two-lever choice procedure. With these animals, we have tested over 100 challenge drugs, at three or more dosage levels, for transfer of stimulus control during extinction. Data for three of these compounds are presented in Table II. These compounds were chosen to emphasize the important point that thorough dose-response tests should be performed in generalization studies. For example, in our initial investigation to assess the ability of the DOM-stimulus to generalize to racemic 1-(3,4-methylendioxyphenyl)-2-aminopropane [methylenedioxyamphetamine (MDA)], we examined in a random sequence the effects of 1.5, 1.75, and 2.50 mg/kg of (±)-MDA. If the investigation had been terminated at this point, it might have been concluded that (±)-MDA does not substitute completely (52%) in DOM-trained animals. However, from our experience in conducting over 300 tests of generalization in animals trained to various hallucinogenic agents, we have found that with some compounds, significant generalization responses can occur within a very narrow range of doses (i.e., some dose-response

Table II
Several Results of Generalization Studies with Racemic DOM (1.0 mg/kg) as the Training Drug

Agent	Dose (mg/kg)	% DOM-appropriate responding
(±)-MDA	1.5	36%
	1.75	52%
	2.0	71%
	2.1	83%
	2.25	Disruption
	2.5	Disruption
R(−)-MDA	0.5	25%
	1.0	60%
	1.5	75%
	1.75	94%
	2.0	Disruption
S(+)-α-MeT	1.25	22%
	1.75	48%
	1.85	59%
	2.0	84%
	2.5	Disruption

curves are quite steep and the generalization "window" quite narrow). Thus, to investigate (±)-MDA more thoroughly we continued the investigation by testing doses of 2.0, 2.1, and 2.25 mg/kg. As can be seen, complete generalization (83%) does occur at 2.1 mg/kg of (±)-MDA.

Also of interest in this dose-response test is the fact that 2.25 and 2.50 mg/kg of (±)-MDA produced disruption of behavior (no responding). When these rats (prior to training) were initially administered the training dose of 1.0 mg/kg of DOM, disruption of behavior was seen. However, after numerous injections, behavioral tolerance to the disruptive effects of the drug was observed. Tolerance to the discriminative stimulus effects was not seen, since the animals could still discriminate between DOM and saline. In the generalization test, the animals were able to respond when administered doses between 1.5 and 2.1 mg/kg of (±)-MDA. Since the administration of 1.5 mg/kg of (±)-MDA to drug-naive animals results in behavioral disruption (Glennon et al., unpublished observation) the results from the discrimination study suggest that there is some cross-tolerance between these agents. However, the behavioral disruption produced by the administration of 2.25 and 2.50 mg/kg of MDA suggests that the animals are not tolerant to these higher doses of (±)-MDA. A similar analysis can be applied to the dose–response data generated from the administration of *R*(−)-MDA and *S*(+)-α-methyltryptamine (Table II).

Besides complete generalization with test compounds, we have observed two other results from generalization studies: partial generalization, and saline-appropriate responding. The training drug may generalize only partially (ca. 40–70%) with the challenge drug after a

thorough dose-response test. That is, the percent drug-lever response is not fully appropriate for either training condition. While data of this kind are the most difficult to interpret, it is our view that partial generalization may occur with test compounds because there are pharmacological effects common to both training drug and challenge drug. Generalization is incomplete, however, because the overlap is less than "perfect." Thus, partial generalization may indicate that low doses of a test compound are similar to low doses of the training drug. However, as the dose is increased, another type of pharmacological effect predominates.

Finally, the administration of various doses of a challenge compound may produce saline-like responding (<20% drug-lever responding). Saline-like responding does not necessarily mean that a challenge drug is inactive, but merely suggests that its effects are dissimilar to those produced by the training dose of the training drug. For example, in rats trained to discriminate racemic DOM (1.0 mg/kg) from saline, Glennon et al.[36] have found that the administration of 1.0 and 1.5 mg/kg of (±)-amphetamine produces saline-like responding, while the administration of 2.0 and 3.0 mg/kg of (±)-amphetamine produces disruption of behavior. It might be speculated that, again, perhaps there is some cross-tolerance between (±)-amphetamine and DOM. However, since the drug-lever percentage is quite low it may be concluded that the stimulus effects are different from that produced by 1.0 mg/kg of DOM. Furthermore, that amphetamine is not actually "saline-like" is supported by the finding that amphetamine itself serves as a training drug in tests of discriminative stimulus control of behavior.[45-47]

2. Antagonism Studies

A particularly effective strategy for elucidating mechanisms involved in the discriminative stimulus properties of various drugs is to investigate agents that antagonize their effects. The rationale behind this procedure is that a training dose of a particular agent will only be blocked by antagonists that somehow interfere with the training drug's mechanism of action (see below). Three approaches can be employed.

With the first approach it may be determined whether the effects of a particular dose of a training drug can be attenuated when various doses of a suspected antagonist are combined with the training stimulus. A dose-response antagonism of the training-drug stimulus will occur in the case of an antagonist blocking the stimulus cue. Alternatively, the dose response of the training drug can be determined both in the presence and absence of a constant dose of the antagonist; with this procedure, a shift of the dose-response curve to the right may occur. A parallel shift to the right is suggestive of a competitive interaction between the training drug agonist and the antagonist. Finally, a more elaborate procedure is to combine various doses of the training drug in combination with various doses of the antagonist. The use of this third approach will generate a series of dose-response agonist–antagonist curves. In this manner, it

may be possible to obtain a more comprehensive picture of the receptor interactions that are occurring.

In common with generalization tests, the results of antagonist tests generally fall into one of three categories; (1) complete antagonism (saline-like responding), (2) partial antagonism (ca. 40–70 drug-lever responding), and (3) drug-like responding (>80% drug-lever responding).

III. DRUG DISCRIMINATION STUDIES INVOLVING HALLUCINOGENIC AGENTS

A. Studies with Specific Hallucinogens

Several hallucinogenic agents have been employed as discriminative stimuli to which animals (primarily rats) have been trained; they include (1) mescaline, (2) lysergic acid diethylamide (LSD), (3) 5-methoxy-*N*,*N*-dimethyltryptamine (5-OMe DMT), and (4) 1-(2,5-Dimethoxy-4-methylphenyl)-2-aminopropane (DOM).Chronologically, mescaline and LSD were the first agents to be studied; many of the early studies in this area sought to establish whether their discriminative stimulus effects were different than those produced by other CNS active agents such as barbiturates, narcotic analgesics, neuroleptics, and various cholinergic agents. Studies of this type have been previously reviewed,[3,37] and for the most part, will not be discussed herein. The results of these early studies revealed that the stimulus properties of hallucinogens differ from those of other classes of CNS-active agents and furthermore, that the discriminative stimulus paradigm is one of the few *in vivo* pharmacological assays that is sensitive and specific enough to distinguish differences even among various hallucinogens.[37] More recent studies with hallucinogenic agents have had three major goals: (a) determination of which agents produce common stimulus effects, (b) elucidation of mechanisms of action, and (c) formulation of *in vivo* structure–activity relationships. These three goals are obviously complimentary to one another, and research done in one area has a direct bearing on the others. Finally, efforts have been made to determine if a relationship exists between the results of various discrimination studies and human hallucinogenic activity/potency. Specific studies involving hallucinogenic agents are described below and are classified according to the agent that was employed as the training drug. The scope of this review is limited to a discussion of classical hallucinogenic/psychotomimetic agents, i.e., derivatives of indolealkylamines (*N*,*N*-dialkyltryptamines, α-alkyltryptamines, LSD derivatives, β-carbolines), phenylkylamines (phenethylamines, phenylisopropylamines), and related compounds.

1. Mescaline

In man, mescaline is only weakly active as a hallucinogenic agent; nevertheless, it does serve as a discriminative stimulus in animals. Hirschhorn and Winter[13] were the first to demonstrate this property for

mescaline hydrochloride. The dose of mescaline and the degree of discrimination varied concomitantly; 5 and 10 μmoles/kg of mescaline prodced saline-like responding, and 20 μmol/kg prodced partial generalization, while doses of 40 (9.9 mg/kg) and 80 μmol/kg were followed by a majority of the animal responses on the mescaline-appropriate lever (i.e., 68% and ca. 90%, respectively). In the same study, LSD was shown to act as a discriminative stimulus; however, the mescaline cue could not be discriminated when paired with LSD, suggesting a similarity of effect. A dose of 9.9 mg/kg of mescaline was determined to be equivalent to 0.12 mg/kg of LSD in terms of its ability to produce discriminated responding when paired with saline. In follow-up studies, Winter sought to test the hypothesis that those pharmacologic properties which distinguish hallucinogens from nonhallucinogens in man might be reflected by different discriminative stimulus properties in rats. 3,4-Dimethoxyphenethylamine hydrochloride (3,4-DMPEA) is a structural analog of mescaline which differs only by lacking a 5-position methoxy group. 3,4-DMPEA is without central or peripheral effects at doses of 400–1000 mg in normal human subjects.[38] Winter[39] and Bueno[40] have both found that the discriminative stimulus effects of mescaline differ from those of 3,4-DMPEA. Another closely related analog is 2,3,4-trimethoxyphenethylamine hydrochloride (2,3,4-TMPEA), a positional isomer of mescaline. Both mescaline (10 mg/kg) and 2,3,4-TMPEA (10 mg/kg) serve as discriminative stimuli when paired with saline; however, in a third group of animals, there was no discriminated responding when mescaline was paired with 2,3,4-TMPEA.[41] These results suggested that both agents are essentially equivalent in terms of potency and in the nature of their discriminative stimulus properties.[41] The assumption was made that 2,3,4-TMPEA was without hallucinogenic activity in man. Thus, this demonstration of similarity of the stimulus properties of these two agents could have far-reaching implications with regards to an understanding of stimulus cues. An evaluation of this assumption now becomes critical. As noted by Winter[41] only a single report exists concerning the human effects of 2,3,4-TMPEA; although this report states that 2,3,4-TMPEA is without hallucinogenic effects in normal subjects, it is unclear as to what doses were employed. Thus, 2,3,4-TMPEA might indeed be inactive in man, but on the other hand, sufficiently high doses may not have been evaluated. Another approach to gaining insight to relative human potency is a comparison of the α-methyl analogs of mescaline (i.e., 3,4,5-TMA) and 2,3,4-TMPEA (i.e., 2,3,4-TMA). α-Methylation of mescaline essentially doubles its human hallucinogenic potency, 3,4,5-TMA being active in man at the 160–200 mg range.[38] Although 2,3,4-TMA has been variously claimed by some to be inactive, and by others to be an active hallucinogen, in fact, this agent has not shown activity in man, but has only been evaluated at total doses of up to 100 mg.[38] To date, the hallucinogenic potency (or lack thereof) of

neither 2,3,4-TMPEA nor 2,3,4-TMA has been reliably established. Thus, additional studies are required, employing agents which are unquestionably without activity in man, in order to further challenge this hypothesis.

Browne et al.[42] have also found that mescaline serves as a discriminative stimulus in rats when paired with saline. However, at the higher training dose of 25 mg/kg, mescaline produced a more rapid, and greater discriminative control of behavior. The mescaline-stimulus generalized to *N,N*-dimethylmescaline in a dose-related manner, although the alkylated derivative was only half as active as mescaline itself. Administration of *N*-monomethylmescaline to the mescaline-trained animals, at doses comparable to those used for *N,N*-dimethylmescaline, failed to produce responding that was significantly different than that produced by saline. Unfortunately, higher doses were not evaluated. Intraventricular administration of mescaline (12.5–50 μg) resulted in partial generalization and in a reduction in response rate. Although generalization was observed when a 75 μg dose was employed, the dramatic reduction in response rate required that the animals remain in their home cages for an additional 15–45 min period before testing, whereupon response rates were somewhat improved.[42] Nevertheless, the generalization produced by intraventricular administration is indicative of a CNS locus for the cueing effect produced by mescaline. *N,N*-Dimethylmescaline (200 and 300 μg), administered via the intraventricular route, produced greater than 70% mescaline-appropriate responding; administration of *N*-monomethylmescaline (50 μg) resulted in a generalization gradient that was not well-defined.

DOM and its homolog 1-(2,5-dimethoxy-4-ethylphenyl)-2-aminopropane (DOET) produced stimulus effects similar to those of mescaline,[43,44] while the effects of cocaine and (+)-amphetamine sulfate were apparently different.[43] Because the effects of DOM in man may differ somewhat from those of DOET, these results, in conjunction with his earlier work, led Winter to conclude that those affects in the rat which function as a discriminative stimulus are better correlated with prehallucinogenic LSD-like activity in man than with hallucinogenic activity per se, and that these effects in rats represent a necessary, but not a sufficient condition for prediction of hallucinogenic activity in man.[43] The above results with (+)-amphetamine are consistent with the findings of Huang and Ho,[45] who reported that an amphetamine stimulus (0.8 mg/kg) mimicked cocaine (7.5 mg/kg), but not DOM (0.25–1.0 mg/kg), DOET (0.25–0.50 mg/kg) nor mescaline (12.5–25 mg/kg). Likewise, Silverman and Ho[46] have reported that mescaline (7.5–22.5 mg/kg) results in less than 37% amphetamine-appropriate responding in rats trained to discriminate (+)-amphetamine (1.0 mg/kg) from saline, while Shannon[47] has found that DOM, at doses of 0.3, 1.0, 3.0, and 10.0 mg/kg, failed to produce greater than 10% amphetamine-appropriate responding.

Studies employing possible metabolites of mescaline, such as 3,4,5-trimethoxyphenylethanol, 3,4,5-trimethoxyphenylacetaldehyde, and *N*-acetyl mescaline, suggest that mescaline itself, and not one of the possible metabolites, is responsible for the stimulus properties produced by mescaline.[48]

2. Lysergic acid diethylamide (LSD)

LSD is the most potent of the known hallucinogens and readily serves as a discriminative stimulus in rats when paired with saline (Table III). As mentioned previously, Hirschhorn and Winter[13] obtained dose-related discriminated responding in animals trained to 0.12 mg/kg of (+)-LSD. Cameron and Appel[49] found that 0.02–0.04 mg/kg of LSD produced a threshold level of discriminability. However, they further found that animals trained to discriminate 0.08 mg/kg of LSD from saline, resulting in 96% LSD-appropriate responding after a dose of 0.08 mg/kg of LSD, and 30% LSD responding after a dose of 0.01 mg/kg of LSD, could be

Table III
Studies Using LSD as a Training Drug

LSD Dose (mg/kg)[a]	Reference[b]
0.12	Hirschhorn and Winter[13]
0.08	Cameron and Appel[49]
0.07	Hirschhorn and Rosecrans[14]
0.029	Hirschhorn and Winter[50]
0.08 (0.01)	Greenberg et al.[32]
0.10	Hirschhorn and Rosecrans[51]
0.08	Kuhn et al.[52]
0.12	Glennon et al.[16]
0.16	Colpaert et al.[53]
0.12	Rosecrans and Glennon[54]
0.10	Winter[55]
0.075[c]	Silverman and Ho[56]
0.10	Winter[57]
0.04	Jarbe[58]
0.05	Jarbe[58]
0.12	White et al.[59]
0.08	Minnema et al.[60]
0.08 (0.02, 0.32)	White and Appel[35]
0.08 (0.02, 0.32)	White and Appel[61]
0.16	Colpaert et al.[62]
0.12	Young et al.[63]
0.08	Appel et al.
0.16	Appel et al.

[a] Dose based on weight of tartrate salt unless otherwise noted. Doses in parenthesis represent fading doses.
[b] Rats were employed in all studies except those of Jarbe, where pigeons were used.
[c] Calculated as weight of free base.

made more sensitive to the LSD cue if 0.01 mg/kg doses were reinforced. That is, these animals could be retrained to discriminate 0.01 mg/kg of LSD such that this dose would elicit greater than 90% LSD-appropriate responding; in animals thusly trained, even a 0.005 mg/kg dose of LSD produced 89% LSD-appropriate responding.[32] These findings support the suggestion by Overton[31] that training dose is important in determining subsequent test dose gradients, and that discriminability is proportional to dose.

Early tests of LSD-stimulus generalization and comparisons of discriminative stimulus properties were not always in complete agreement with one another; some of these results have been previously reviewed by Kuhn et al.[37] Often, doses of LSD were reported in molar units, and this may be one source of conflict. The LSD currently available (via Sandoz Pharmaceuticals) is the tartrate monomethanolate salt, i.e., two molecules of LSD, one of tartaric acid, with a molecule of methanol of crystallization. As such, the molecular weight of this substance is 829; it is evident that in the past this molecular weight was not always employed in conversion of microgram doses to micromolar doses (if one assumes that all studies were conducted with LSD from the same source).

Although LSD has been the object of numerous discrimination studies, relatively little has been reported with respect to stimulus generalization experiments. LSD-stimulus generalization has been demonstrated for mescaline[49] and for 5-OMe DMT.[16,35,54,63] At an LSD training dose of 0.12 mg/kg, the ED_{50} of 5-OMe DMT is 0.76 mg/kg (Glennon et al., unpublished results). *l*-LSD, a "nonhallucinogenic" isomer of LSD, produced saline-like responding when administered at a dose equivalent to the training dose of LSD (i.e., 0.08 mg/kg) at a higher dose (0.25 mg/kg) of *l*-LSD, an increase in LSD-appropriate responding was observed.[49] Silverman and Ho[56] found that R(−)-, S(+)- and racemic DOM, (±)-DOB and (±)-2,4,5-TMA, but not (+)-amphetamine, produced greater than 80% LSD-appropriate responding; ranked in order of potency, DOB > R(−)-DOM > (±)-DOM > S(+)-DOM > 2,4,5-TMA. Recently, White and Appel[35] have found, using LSD training doses of 0.02, 0.08, and 0.32 mg/kg, that stimulus generalization occurs with 5-OMe DMT (free base) in all three groups of animals, but that generalization does not occur with the dopamine agonist apomorphine hydrochloride, nor with (+)-amphetamine sulfate. This latter finding with amphetamine is consistent with the earlier results of Cameron and Appel,[43] and with the results of Shannon,[47] who found that an amphetamine stimulus did not generalize with LSD. 5-Methoxytryptamine (5 mg/kg) produced 70% LSD-appropriate responding in LSD-trained (0.02 mg/kg) animals; responding after 1.25–10.0 mg/kg of 5-methoxytryptamine in the animals trained to 0.08 and 0.32 mg/kg of LSD was essentially saline-like.[35] Because 5-methoxytryptamine does not readily penetrate the blood–brain barrier, the authors suggest that the low-dose LSD cue may have a peripheral

component. LSD-stimulus generalization has also been shown to occur with quipazine,[35,53,55,62,64] mescaline,[53,62] the α-ethyl homolog of DOM (i.e., BL-3912),[57] psilocybin,[58] DMT,[58] but not with fenfluramine[57] or Δ^9-THC.[58]

White and Appel[61] have recently reported the results of a very interesting study comparing the discriminative stimulus properties of LSD with those of a structurally related but presumably nonhallucinogenic ergot derivative lisuride. The neurotransmitter serotonin has been implicated as playing a role in the mechanism of action of LSD and several other hallucinogenic agents. However, distinct similarities exist for the effects of LSD and lisuride on various serotonergic functions. To examine this problem, White and Appel[61] trained groups of animals (rats) to discriminate LSD from saline, and lisuride from saline, at doses of 0.02, 0.08, and 0.32 mg/kg; subsequent generalization studies revealed similarities in the discriminative stimulus properties of these agents. In a companion study, three groups of rats were trained to discriminate LSD (0.08 mg/kg) from lisuride (0.02, 0.04, and 0.08 mg/kg). Substitution tests were then conducted with saline, LSD, lisuride, the purported serotonin agonist quipazine, and the dopamine agonist apomorphine. In tests with relatively high doses of lisuride, in the group of animals trained at 0.08 mg/kg of lisuride, responding occurred on the lisuride-appropriate lever; however, with low doses of lisuride, responding occurred on the LSD-appropriate lever. In the other groups of animals, discriminations were based on qualitative differences. Furthermore, quipazine was found to elicit LSD-appropriate responding while apomorphine produced responding appropriate for lisuride. While the authors emphasize that the results do not necessarily mean that LSD and lisuride act only at serotonin and dopamine receptors, respectively, they do suggest that the discriminative stimulus effects of these agents are mediated primarily by actions on one or the other of these neuronal systems.[61] These findings are in concert with an earlier suggestion by Glennon and Rosecrans[65] that psychoactive drugs probably interact with more than one amine system *in vivo*, but that one system may predominate in terms of an animal's ability to discriminate a given agent or chemical structure.

3. *5-Methoxy-N,N-dimethyltryptamine (5-OMe DMT)*

The discriminative stimulus properties of indolealkylamines other than LSD have only been investigated to a limited extent. For example, Frey and Winter[66] have shown that both *N,N*-diethyltryptamine (DET) and 6-fluoro DET can serve as discriminative stimuli when paired with saline. Psilocybin serves as a discriminable stimulus when paired with Δ^9-THC,[67] and when paired with saline.[68] With the exception of 5-methoxy-*N,N*-dimethyltryptamine (5-OMe DMT), however, detailed studies involving indolealkylamines (or tryptamine derivatives) as the training drug have been lacking. Rats are able to discriminate the

hallucinogenic agent 5-OMe DMT hydrogen oxalate from saline; several different training doses have been employed by Glennon and co-workers including 1.0 mg/kg,[16,69] 1.5 mg/kg,[16,54,70] and 3.0 mg/kg.[63,71]

The indolealkylamine hallucinogen 5-OMe DMT, like the phenalkylamine hallucinogen DOM, possesses a relatively high affinity for the serotonin receptors of the isolated rat fundus preparation. In order to further explore a role for serotonin in the mechanism of action of these two agents, and in order to propose comparative structure–affinity relationships between these two classes of hallucinogenic agents, it was important to determine if members of these two classes were capable of producing similar behavioral (stimulus) effects. Thus, the first study using 5-OMe DMT as a discriminative stimulus was directed toward this goal; indeed, the 5-OMe DMT-stimulus (1.0 mg/kg) was found to generalize to DOM in a dose-related manner.[16,69] Because serotonin receptor affinity data were available for several other indolealkylamine and phenalkylamine derivatives, additional studies were conduced in order to determine (a) whether 5-OMe DMT-stimulus generalization would occur with these agents, and (b) whether or not a relationship might exist between serotonin receptor affinity and the ED_{50} values of those agents to which the 5-OMe DMT stimulus generalized. Initial results revealed (Fig. 4) that 5-OMe DMT-stimulus (1.5 mg/kg) generali-

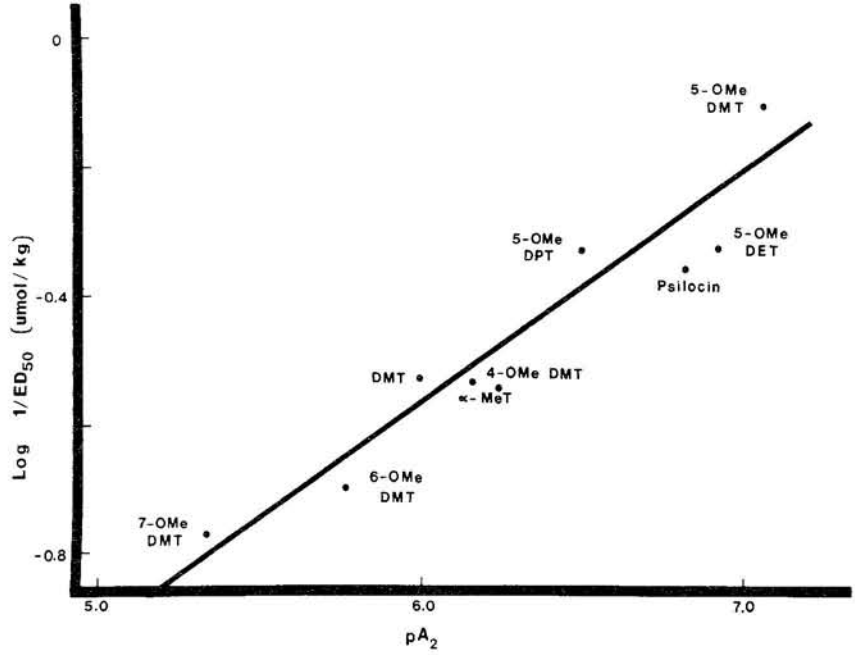
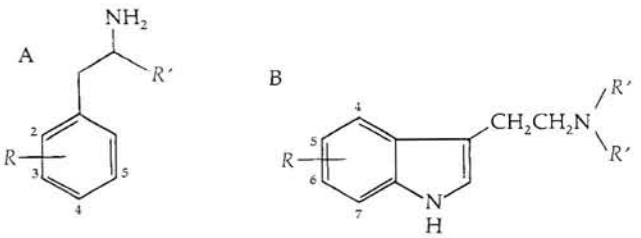


Figure 4. Relationship between the serotonin receptor affinity (pA_2) and discrimination-derived ED_{50} values (using rats trained to discriminate 1.5 mg/kg of 5-OMe DMT from saline) for nine indolealkylamine derivatives.

zation occurred with 5-OMe DPT, psilocin (4-OH DMT), 5-OMe DET, α-methyltryptamine (α-MET), DMT, 4-OMe DMT, 6-OMe DMT, and 7-OMe DMT, and that the more active agents possessed a higher serotonin receptor affinity than the lesser active agents. These findings were later extended to include several other agents including DOM, 2,5-DMA, 5-TMT, 7-TMT, 1-TMT, and 3,4,5-TMA.[70] Subsequent studies revealed that the 5-OMe DMT (1.5 mg/kg) stimulus also generalized, in a dose-related manner, to the hallucinogens LSD and mescaline, as well as to a number of other indolealkylamine and phenalkylamine derivatives (Table IV). Although 5-OMe DMT (1.5 mg/kg) and DOM apparently produce similar discriminative stimulus properties, the 5-OMe DMT stimulus did not generalize to a series of DOM homologs; data for these and several other compounds are shown in Table IV. The question has often been raised as to whether hallucinogens and nonhallucinogens produce similar discriminative stimuli in animals, however, another question seems to have been overlooked, i.e., do results from discrimination studies parallel human hallucinogenic data. Figure 5 shows that there is at least a loose correlation between ED_{50} values from the discrimination studies, using 5-OMe DMT (1.5

Table IV
Results of some Generalization Studies Using 5-OMe DMT (1.5 mg/kg) as the Training Drug



A. Results with phenalkylamine derivatives

	R'	R_2	R_3	R_4	R_5	Result[a]	Reference[b]
(±)-Amphetamine	Me	H	H	H	H	D[c]	U
(±)-4-Me PIA	Me	H	H	Me	H	D[c]	U
(±)-2,5-DMA	Me	OMe	H	H	OMe	0.59	72
(±)-DOM	Me	OMe	H	Me	OMe	0.46	72
(±)-2-HMP	Me	OH	H	H	OMe	0.70	72
(±)-2-HMMP	Me	OH	H	Me	OMe	2.46	72
(±)-5-HMMP	Me	OMe	H	Me	OH	D	72
(±)-DOET	Me	OMe	H	Et	OMe	D	73
(±)-DOPR	Me	OMe	H	nPr	OMe	D	73
(±)-DOBU	Me	OMe	H	nBu	OMe	D	73
(±)-DOTB	Me	OMe	H	tBu	OMe	D	73
(±)-DOAM	Me	OMe	H	nAm	OMe	D	73
Mescaline	H	H	OMe	OMe	OMe	12.29	70

Table IV
Continued

B. Results with indolealkylamine derivatives

	R'	R_4	R_5	R_6	R_7	Result[a]	Reference[b]
Tryptamine	H	H	H	H	H	S (11%/12.0)	U
5-OMeT	H	H	OMe	H	H	D[d]	U
Psilocin	Me	OH	H	H	H	0.48	U
4-OMe DMT	Me	OMe	H	H	H	1.07	74
4-SMe DMT	Me	SMe	H	H	H	3.10	74
5-OMe DMT	Me	H	OMe	H	H	0.40	U
5-SMe DMT	Me	H	SMe	H	H	0.48	74
5-OMe 6-TMT	Me	H	OMe	Me	H	S (0%/4.0)	75
5-OMe 7-TMT	Me	H	OMe	H	Me	1.54	75
5,7-diOMe DMT	Me	H	OMe	H	OMe	3.38	75
6-TMT	Me	H	H	Me	H	S (0%/5.0)	75
7-TMT	Me	H	H	H	Me	0.64	75
DMT	Me	H	H	H	H	0.74	70
5-OMe DPT	nPr	H	OMe	H	H	0.78	70
5-OMe DIPT	iPr	H	OMe	H	H	0.84	70
5-OMe DET	Et	H	OMe	H	H	0.72	70
7-Et DMT	Me	H	H	H	Et	D	75
7-Br DMT	Me	H	H	H	Br	D	75
LSD	—	—	—	—	—	0.03	U

[a]Where 5-OMe DMT-stimulus generalization occurred, ED_{50} values are reported in mg/kg. Those agents producing saline-like responding, followed by disruption of behavior at higher doses, are designated by D. Agents producing saline-like responding at the highest dose tested are represented by S, followed by percent 5-OMe DMT-appropriate responding and highest dose tested.

[b]Reference: U = unpublished data from our laboratories.

[c]Amphetamine and 4-Me PIA both produced saline-like responding at doses below about 1 mg/kg, and produced disruption of behavior at higher doses.

[d]5-OMeT produced 16% 5-OMe DMT-appropriate responding at 0.5 mg/kg, 24% at 1.0 mg/kg, and disruption of behavior at 2.0 and 4.0 mg/kg.

mg/kg) as the training drug, and the human hallucinogenic potency of mescaline, DMT, α-MeT, psilocin, 5-OMe DIPT, DOM, 5-OMe DMT, and LSD.

Numerous phenalkylamine derivatives are psychoactive in man[38]; in both human and animal studies, these agents produce effects which are amphetamine-like and/or LSD-like.[77,78] The unsubstituted phenalkylamine derivative amphetamine hydrochloride (PIA) possesses a relatively low affinity for the serotonin receptors of the rat fundus, i.e., approximately one-onehundredth that of DOM. DOM, but not amphetamine, apparently produces stimulus effects similar to those produced by 5-OMe DMT. Even though all of the phenalkylamines are somewhat structurally related, the possibility exists that the mechanism of action, and indeed the behavioral effects, of those agents with a high serotonin receptor affinity might differ from those with a lower affinity. There-

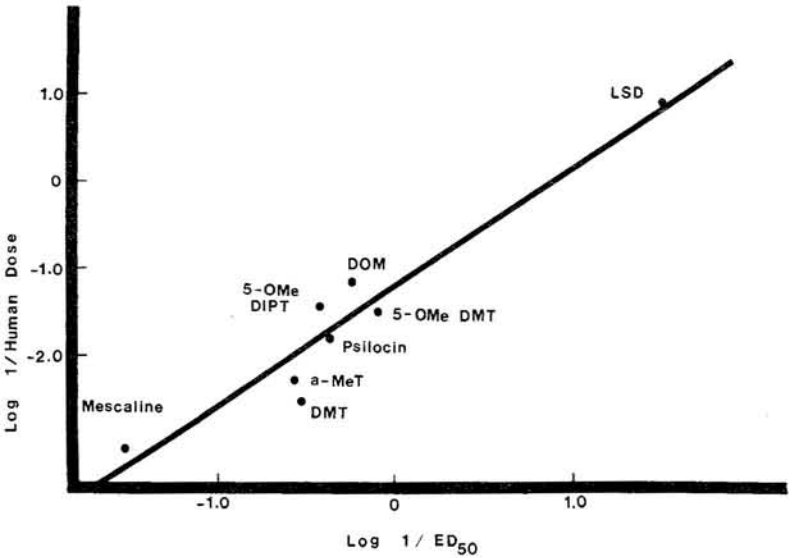


Figure 5. Relationship between the human hallucinogenic potency (log 1/total dose in micromoles) and ED_{50} values (log $1/ED_{50}$ in micromoles/kg) for several hallucinogenic agents using 5-OMe DMT as the training drug.

fore, an investigation was undertaken in order to determine which of a series of phenalkylamines was capable of producing effects similar to those of 5-)Me DMT. The training dose employed for 5-OMe DMT was 3.0 mg/kg; the phenalkylamines included 36 phenylisopropylamines and/or isomers.[71] The results of this study allowed the differentiation of phenalkylamine derivatives on the basis of their stimulus properties. The 5-OMe DMT stimulus generalized to those agents in Table V(A); thus, it might be inferred that these phenalkylamines are capable of producing interoceptive cues similar to the cue produced by 3.0 mg/kg of 5-OMe DMT. With the exception of 6-Me, 2,4-DMA, for which human data are unavailable, those agents listed in Table V(A) have all been demonstrated to be hallucinogenic in man. Several agents, notably 2,6-DMA, 3,5-DMA, 2,3,4-TMA, and 2,3,5-TMA produced saline-like responding at their highest dose tested (7–9 mg/kg). The remaining 23 compounds either (a) produced partial generalization (40–67% 5-OMe DMT-appropriate) at low doses, or (b) produced saline-like (5–35% 5-OMe DMT-appropriate) responding at low doses. In both cases, however, slight increases in dosage resulted in disruption of behavior (Table V). In general, those agents to which the 5-OMe DMT cue generalized possessed greater serotonin receptor affinities than those for which generalization was not observed.

4. *1-(2,5-Dimethoxy-4-methylphenyl)-2-aminopropane (DOM)*

In 1975, Tilson et al.[79] trained rats to discriminate 0.75 mg/kg of *R*(−)-1-(2, 5-dimethoxy-4-methylphenyl)-2-aminopropane, i.e., *R*(−)-

Table V
Results of Generalization Studies with Phenalkylamines Using 5-OMe DMT (3.0 mg/kg) as the Training Drug[a,b]

A. Agents to which the 5-OMe DMT stimulus generalized

Agent	ED_{50} (mg/kg)
R(−)-DOM	0.38
(±)-DOM	0.49
R(−)-MDA	0.85
(±)-MDA	1.05
(±)-2-OMe 4,5-MDA	2.45
(±)-2,5-DMA	2.42
(±)-2,4,6-TMA	3.00
(±)-4-Me, 2,6-DMA	2.25
(±)-6-Me 2,4-DMA	2.48

B. Agents that produced partial generalization, followed by disruption of behavior at higher doses

(±)-MMA	(±)-2,3-DMA	(±)-DOB
(±)-PMA	(±)-3,4,5-TMA	(±)-3-Me 2,5-DMA
R(−)-PMA		

C. Agents that produced saline-like responding, followed by disruption of behavior at higher doses

(±)-OMA	(±)-DOET	(±)-3-Br 2,5-DMA
S(+)-PMA	*R*(−)-DOET	(±)-2-OEt 4,5-DMA
S(+)-DOM	*S*(+)-DOET	(±)-4-OEt 2,5-DMA
S(+)-MDA	(±)-3,4-DMA	(±)-5-OEt 2,4-DMA
(±)-2,4-DMA	(±)-2,3,4-TMA	(±)-Amphetamine
	(±)-cathinone	

[a] Data from reference 71.
[b] See Table VII for structures.

DOM, from saline. In a parallel study, a second group of animals was trained to discriminate 1.0 mg/kg of *S*(+)-amphetamine from saline. Administration of 0.5–1.5 mg/kg of *R*(−)-DOM to the DOM-trained animals produced dose-related discriminated responding; higher doses (2.2 mg/kg) resulted in random responding. Administration of low doses of *R*(−)-DOM to the amphetamine-trained animals resulted in 68–69% amphetamine-appropriate responding, while administration of low doses of *S*(+)-amphetamine to the DOM-trained animals resulted in 69–80% DOM-appropriate responding. The authors concluded that low doses of *R*(−)-DOM were capable or producing discriminative stimulus effects dissimilar to higher doses of *R*(−)-DOM, but similar to low doses of amphetamine.[79] These findings appear to be in conflict with more recent results. (+)-Amphetamine-stimulus generalization does not occur to racemic DOM over a large range of doses,[47] and DOM-stimulus generalization does not result when animals are administered amphetamine.[36]

Although the last two studies employed racemic DOM, Silverman and Ho[33,46] have found that a (+)-amphetamine stimulus cue apparently differs from that produced by either racemic, *R*(−)- or *S*(+)-DOM. The latter authors suggest that the particular testing schedule employed in the Tilson study might have biased the animals lever choice.[33] It might also be noted that the animals in the Tilson study, which were trained to discriminate *R*(−)-DOM from saline or (+)-amphetamine from saline still responded 30–40% on the drug-appropriate lever after administration of saline.

Silverman and Ho[33] demonstrated that 0.75 mg/kg of racemic DOM, like *R*(−)-DOM, also served as a discriminative stimulus in rats when paired with saline. Administration of mescaline (18.0 mg/kg) resulted in DOM-stimulus generalization, however, half of the animals failed to respond. Subsequently, the animals were faded or "trained down" to discriminate 0.5 mg/kg of DOM from saline and DOM-stimulus generalization was found to occur with mescaline (12.0 mg/kg), with 90% of the animals now responding. Although only one dose was tested, LSD (0.08 mg/kg) produced 70% DOM-appropriate responding. Neither (+)-amphetamine, phencyclidine (PCP), nor Δ^9-THC produced significant DOM-appropriate responding.[33]

In a later study, Silverman and Ho[46] used 1.5 mg/kg of racemic DOM as the training drug. The DOM stimulus generalized to both optical isomers of DOM, mescaline, racemic DOET, but not to (+)-amphetamine, 4-methylamphetamine or methylphenidate; at doses of 1.0 and 1.5 mg/kg psilocybin produced 74% and 71% DOM-appropriate responding. Some of these results are summarized in Table VI.

Young et al.[12] trained animals (rats) to discriminate 1.0 mg/kg of DOM from saline. Consistent with human studies, DOM was found to possess a relatively long duration of action. After a 15-min presession injection interval, administration of DOM (1.0 mg/kg) produced an average of 96% DOM-appropriate responding; with presession intervals of 120 and 180 min, percent DOM-appropriate responding was still approximately 70%

Table VI
Selected Results of a Generalization Study Using DOM (1.5 mg/kg) as the Training Drug[a]

Agent	Highest dose tested (mg/kg)	% DOM-appropriate responding
Mescaline	15.0	86%
R(−)-DOM	0.75	100%
S(+)-DOM	2.25	84%
(±)-DOET	0.75	83%
Psilocybin	1.0	74%
(±)-2,5-DMA	8.0	72%

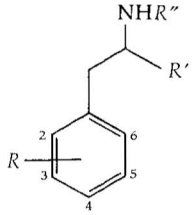
[a]Data from Silverman and Ho.[46]

and 50%, respectively. After 240 min, 1.0 mg/kg of DOM produced saline-like responding.[12] Stimulus generalization occurs between DOM and 5-OMe DMT regardless of which is used as the training drug.[12,16] Evidently, DOM and 5-OMe DMT produce similar interoceptive cues, yet while the DOM stimulus generalizes to DOET,[46] the 5-OMe cue doesn't generalize to DOET or any other of the DOM homologs.[73] It appears that DOM and 5-OMe DMT possess common stimulus qualities that are not shared by certain phenalkylamine derivatives. As such, it was felt that DOM-trained animals might be better suited than 5-OMe DMT-trained animals for exploring the stimulus effects of various phenalkylamines. Accordingly, the next two studies involving DOM-trained animals were concerned with minor structural modifications of the DOM molecule, and with the aforementioned series of DOM homologs.[80,81] Several subsequent studies investigated the stimulus properties of an additional 50 phenalkylamine derivatives.[36,82–85] Now that a considerable body of data have been collected (Table VII), structure–activity relationships for hallucinogenic agents can be formulated, for the first time, on the basis of their stimulus properties. The remainder of this section will review the structure–activity relationships of various hallucinogenic agents which have been administered to DOM-trained rats. Because these studies involved an *in vivo* assay, the results reflect the overall consequence of metabolism, distribution etc., and the proposed structure–activity interpretations might not necessarily parallel those derived from various *in vitro* studies. On the other hand, it is possible that similarities might exist between these relationships and those derived from other *in vivo*, including human, studies. With respect to the discrimination studies, the agents were administered to the DOM-trained rats in a dose-related manner; doses were administered, for the most part, in a random order. At the highest dose tested, any one of three possible eventualities were observed: (a) stimulus generalization, (b) disruption of behavior (without prior generalization), or (c) saline-like responding. In all cases, response rates were not significantly different under drug or nondrug (saline) conditions, except where complete disruption of behavior (i.e., no responding) occurred. When generalization occurred, ED_{50} values were determined. As discussed in Sec. II, B 3, it has been noted that dose-response gradients for drug discriminability are largely determined by training dose. Thus, dose-response curves represent relative, not absolute, relationships between test dose and training dose. It is thus emphasized that the ED_{50} values reproduced in Table VII are relative to a DOM training dose of 1.0 mg/kg, and that a 15-min presession injection-interval was used throughout.

a. Phenylisopropylamine Derivatives. Administration of low doses of amphetamine, or any of its monomethoxy derivatives (i.e., OMA, MMA, and PMA), to the DOM-trained animals resulted in either saline-like or random responding; slight increases in dose resulted in disruption of

Table VII

Results of Generalization Studies on Phenalkylamines using DOM-Trained (1.0 mg/kg) Rats



Agent	R'	R''	R_2	R_3	R_4	R_5	R_6	Reference	Result[a]
(±)-Amphetamine	Me	H	H	H	H	H	H	36	D
(±)-OMA	Me	H	OMe	H	H	H	H	36	D
(±)-MMA	Me	H	H	OMe	H	H	H	36	D
(±)-PMA	Me	H	H	H	OMe	H	H	36	D
R(−)-PMA	Me	H	H	H	OMe	H	H	36	D
(±)-2,3-DMA	Me	H	OMe	OMe	H	H	H	83	D
(±)-2,4-DMA	Me	H	OMe	H	OMe	H	H	83	4.88
(±)-2,5-DMA	Me	H	OMe	H	H	OMe	H	80	5.51
R(−)-2,5-DMA	Me	H	OMe	H	H	OMe	H	80	3.25
S(+)-2,5-DMA	Me	H	OMe	H	H	OMe	H	80	D
(±)-2,6-DMA	Me	H	OMe	H	H	H	OMe	83	D
(±)-3,4-DMA	Me	H	H	OMe	OMe	H	H	82	D
(±)-3,5-DMA	Me	H	H	OMe	H	OMe	H	83	D
(±)-2,3,4-TMA	Me	H	OMe	OMe	OMe	H	H	83	7.80
(±)-2,3,5-TMA	Me	H	OMe	OMe	H	OMe	H	83	16.48
(±)-2,4,5-TMA	Me	H	OMe	H	OMe	OMe	H	36	3.59
(±)-2,4,6-TMA	Me	H	OMe	H	OMe	H	OMe	83	3.69
(±)-3,4,5-TMA	Me	H	H	OMe	OMe	OMe	H	83	6.34
(±)-DOM	Me	H	OMe	H	Me	OMe	H	12	0.44

R(−)-DOM	Me	H	OMe	H	Me	OMe	H	80	0.21
S(+)-DOM	Me	H	OMe	H	Me	OMe	H	80	1.70
(±)-DOET	Me	H	OMe	H	Et	OMe	H	36	0.23
R(−)-DOET	Me	H	OMe	H	Et	OMe	H	81	0.09
S(+)-DOET	Me	H	OMe	H	Et	OMe	H	81	0.85
(±)-DOPR	Me	H	OMe	H	nPr	OMe	H	81	0.17
(±)-DOBU	Me	H	OMe	H	nBu	OMe	H	81	0.91
(±)-DOTB	Me	H	OMe	H	tBu	OMe	H	81	D
(±)-DOAM	Me	H	OMe	H	nAm	OMe	H	81	D
(±)-DOF	Me	H	OMe	H	F	OMe	H	36	1.45
(±)-DOB	Me	H	OMe	H	Br	OMe	H	36	0.20
R(−)-DOB	Me	H	OMe	H	Br	OMe	H	36	0.10
S(+)-DOB	Me	H	OMe	H	Br	OMe	H	36	0.81
(±)-DOI	Me	H	OMe	H	I	OMe	H	36	0.42
R(−)-DOI	Me	H	OMe	H	I	OMe	H	36	0.26
(±)-DON	Me	H	OMe	H	NO_2	OMe	H	36	0.76
R(−)-DON	Me	H	OMe	H	NO_2	OMe	H	36	0.57
(±)-3-Me-2,5-DMA	Me	H	OMe	Me	H	OMe	H	80	S (34%/8.0)
(±)-3-Br-2,5-DMA	Me	H	OMe	Br	H	OMe	H	36	S (0%/3.0)
(±)-MDA	Me	H	H	H	$O\text{-}CH_2\text{-}O$		H	82	1.68
R(−)-MDA	Me	H	H	H	$O\text{-}CH_2\text{-}O$		H	82	0.81
S(+)-MDA	Me	H	H	H	$O\text{-}CH_2\text{-}O$		H	82	D
(±)-2-OMe-MDA	Me	H	OMe	H	$O\text{-}CH_2\text{-}O$		H	82	3.36
(±)-5-Me-2,4-DMA	Me	H	OMe	H	OMe	Me	H	83	3.18
(±)-5-OEt-2,4-DMA	Me	H	OMe	H	OMe	OEt	H	83	10.15
(±)-5-Br-2,4-DMA	Me	H	OMe	H	OMe	Br	H	83	6.69
(±)-6-Me-2,4-DMA	Me	H	OMe	H	OMe	H	Me	83	3.46
(±)-4-OEt-2,5-DMA	Me	H	OMe	H	OEt	OMe	H	83	6.33
(±)-3OMe-MD	Me	H	H	H	OH	OMe	H	82	S (7%/18.0)
(±)-2-HMMP	Me	H	OH	H	Me	OMe	H	80	1.71
(±)-5-HMMP	Me	H	OMe	H	Me	OH	H	80	D
(±)-PMP	Me	H	OMe	OMe	OMe	OMe	OMe	b	D
(±)-N-Me DOM	Me	Me	OMe	H	Me	OMe	H	85	3.99

Table VII
(Continued)

Agent	R'	R''	R_2	R_3	R_4	R_5	R_6	Reference	Result[a]
R(−)-N-Me DOM	Me	Me	OMe	H	Me	OMe	H	85	2.59
(±)-MDMA	Me	Me	H	H	O-CH_2-O		H	82	D
R(−)-MDMA	Me	Me	H	H	O-CH_2-O		H	82	D
S(+)-MDMA	Me	Me	H	H	O-CH_2-O		H	82	D
HPA	H	H	H	H	O-CH_2-O		H	82	S (12%/12.0)
α-deMe DOM	H	H	OMe	H	Me	OMe	H	85	1.31
Mescaline	H	H	H	OMe	OMe	OMe	H	83	14.64

[a]Results of discrimination study using 1.0 mg/kg of DOM hydrochloride as the training drug. Where DOM-stimulus generalization occurred, ED_{50} values are reported in mg/kg. Those agents producing saline-like effects or partial generalization, followed by complete disruption of behavior at higher doses are designated by D. Agents producing saline-like effects at their highest dose evaluated are represented by S, followed by, in parenthesis, the highest % DOM-appropriate responding observed and the dose that produced this result.
[b]Glennon, Young, Benington, and Morin, unpublished data.

behavior. Apparently, neither amphetamine or any of its monomethoxy derivatives produce stimulus effects similar to those of DOM. The results with amphetamine are consistent with those reported by Silverman and Ho.[46] There exists six possible dimethoxyphenylisopropylamine (DMA) derivatives (i.e., 2,3-DMA, 2,4-DMA, 2,5-DMT, 2,6-DMA, 3,4-DMA, and 3,5-DMA); DOM-stimulus generalization occurred only with 2,4-DMA and 2,5-DMA. The ED_{50} values of these two agents (4.88 and 5.51 mg/kg, respectively) were similar. Of the trimethoxyphenylisopropylamines (i.e., TMA derivatives) evaluated, all resulted in stimulus generalization. The two most active derivatives, 2,4,5-TMA and 2,4,6-TMA, were more active than either 2,4-DMA or 2,5-DMA; both possess the 2,4-dimethoxy substitution pattern.

DOM may be considered as the methyl homolog of 2,5-DMA; further homologation affords DOET, DOPR, DOBU, and DOAM. Homologation tends to enhance potency in the order: 2,5-DMA < DOM < DOET < DOPR. As the size of the alkyl group is increased to butyl, as in DOBU, activity begins to decline, until, with the tertiary butyl (DOTB) and amyl (DOAM) derivatives, DOM-stimulus generalization is no longer observed. In general, substitution at the 4-position of 2,5-DMA with functions other than alkyl groups also results in rather potent analogs. Of these, the most potent is the 4-bromo derivative DOB; activity decreases in the order Br (DOB) > I (DOI) > NO_2 (DON) > F (DOF). Interestingly, repositioning the methyl group of DOM, or the bromo group of DOB, from the 4- to the 3-position (i.e., 3-Me 2,5-DMA and 3-Br 2,5-DMA, respectively) results in a dramatic decrease in activity. At 15–20 times the ED_{50} dose of DOM or DOB, these repositioned isomers produced less than 35% DOM-appropriate responding.

In addition to 2,5-DMA, the only other dimethoxy derivative to which the DOM stimulus generalized was 2,4-DMA. 2,4-DMA derivatives are a relatively unexplored class of compounds and only a few such derivatives are currently available. Nevertheless, all four compounds evaluated (i.e., 5-Me 2,4-DMA, 5-OEt 2,4-DMA, 5-Br 2,4-DMA, and 6-Me 2,4-DMA) resulted in DOM-stimulus generalization. The further evaluation of agents bearing this substitution pattern certainly appears warranted.

N-Alkylated phenylisopropylamines is another class of compounds that has received relatively little attention. Racemic 3,4-methylenedioxyphenylisopropylamine (MDA) produces stimulus effects similar to those of DOM, however, administration of its *N*-methyl derivative, racemic MDMA, to the DOM-trained animals results in disruption of behavior. On the other hand, DOM-stimulus generalization occurred with the *N*-methyl derivative of DOM (i.e., N-Me DOM), although it possesses only one-tenth the activity of the parent compound.

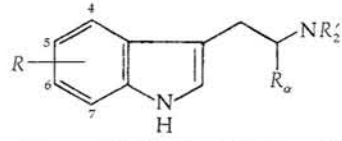
b. Phenylisopropylamine Optical Isomers. The stimulus properties of a

number of optical isomers of substituted phenylisopropylamines have been investigated. Silverman and Ho[46] had already reported that *R*(−)-DOM was more active than *S*(+)-DOM in DOM-trained animals. The results shown in Table VII are consistent with their findings. In general, where stimulus generalization was observed with racemates, the *R*(−)-isomers were found to be more active than either the *S*(+)-enantiomers and/or the racemic mixtures, e.g., with DOM, 2,5-DMA, DOET, MDA, DOB, DOI, or DON. In some instances, administration of *R*(−)-isomers resulted in stimulus generalization, whereas the corresponding *S*(+)-enantiomers produced disruption of behavior. Thus, it appears that the *R*(−)-isomers of 2,5-DMA and MDA, for example, endow their racemates with DOM-like properties, while *S*(+)-2,5-DMA and *S*(+)-MDA apparently produce stimulus effects that are dissimilar to those produced by DOM.

c. Phenethylamine Analogs. Very few phenethylamines have been examined. Mescaline, for example, produces DOM-like stimulus effects, but is only weakly active (ED_{50} = 14.64 mg/kg); the potency of mescaline is between one-half and one-third that of its α-methyl (i.e., phenylisopropylamine) counterpart. 3,4-Methylenedioxyphenethylame, the α-demethyl analog of MDA, at seven times the ED_{50} does of (±)-MDA, produces only 12% DOM-appropriate responding. Removal of the α-methyl group of DOM, to afford its phenethylamine counterpart (ED_{50} = 1.51 mg/kg), resulted in a threefold decrease in potency. Before any general statement can be made regarding the effect of removing the α-methyl group of phenylisopropylamines (resulting in phenethylamines), it will be necessary to study additional analogs. Nevertheless, based on very limited data, it appears as though the phenethylamines are less active than their corresponding phenylisopropylamines.

d. Indolealkylamine Derivatives. Some of the data obtained for indolealkylamine derivatives are shown in Table VIII. Neither tryptamine (13% DOM-appropriate responding at 25 mg/kg) nor 5-methoxytryptamine (disruption of behavior at 2.5 mg/kg) produced stimulus effects similar to 1.0 mg/kg of DOM. Experimental evidence suggests that such compounds do not readily penetrate the blood–brain barrier.[86–88] However, DOM-stimulus generalization did occur to both *N*,*N*-dimethyltryptamine (DMT) and 5-OMe DMT, as well as to α-MeT and 5-OMe α-MeT. In both cases, the α-methyl derivatives were about twice as active as their *N*,*N*-dimetyl analogs. α-Methyltryptamine and 5-OMe α-MeT were resolved and their individual optical isomers examined (Fig. 6). Clearly, DOM-like properties reside with the *s*(+)-isomers of both α-methyl derivatives. The most potent indolealkylamine, and, indeed, the most potent copound to be evaluated was (+)-LSD (ED_{50} = 0.052 mg/kg). The DOM-stimulus has also been found to generalize with other indolealkylamines such as 6-methoxy *N*-isoDMT (ED_{50} = 7.11 mg/kg) and 6-methoxyharmalan (ED_{50} = 5.13 mg/kg) (Glennon et al., unpublished

Table VIII
Results of Generalization Studies with Indolealkylamine Derivatives
Using DOM (1.0 mg/kg) as the Training Drug



Agent	R_α	R'	R	Result[a]
Tryptamine	H	H	H	S (13%/25.0)
5-OMeT	H	H	5-OMe	D (12%/2.25)
DMT	H	Me	H	5.80 mg/kg
4-OMe DMT	H	Me	4-OMe	3.53 mg/kg
5-OMe DMT	H	Me	5-OMe	1.22 mg/kg
6-OMe DMT	H	Me	6-OMe	S (9%/10.0)
4-TMT	H	Me	4-Me	2.49 mg/kg
7-TMT	H	Me	7-Me	4.89 mg/kg
5-OMe-7-TMT	H	Me	5-OMe 7-Me	1.12 mg/kg
DET	H	Et	H	2.45 mg/kg
5-OMe DET	H	Et	5-OMe	0.75 mg/kg
DPT	H	nPr	H	2.20 mg/kg
DIPT	H	iPr	H	2.60 mg/kg
5-OMe DIPT	H	iPr	5-OMe	1.06 mg/kg
(±)-α-MeT	Me	H	H	3.13 mg/kg
(+)-α-MeT	Me	H	H	1.64 mg/kg
(−)-α-MeT	Me	H	H	D (61%/3.25)
(±)-5-OMe α-MeT	Me	H	5-OMe	0.52 mg/kg
(+)-5-OMe α-MeT	Me	H	5-OMe	0.21 mg/kg
(−)-5-OMe α-MeT	Me	H	5-OMe	0.92 mg/kg
(±)-α-EtT	Et	H	H	6.62 mg/kg
(+)-LSD				0.052 mg/kg

[a]Where generalization occurred, ED_{50} dose is given. Where saline-like (S) or disruption of behavior (D) was observed, maximal percent DOM-appropriate responding, and dose that produced that result, are given in parenthesis.

observation). Thus, several indolealkylamines, incuding α-methyltryptamines, dialkyltryptamines, *N*-isotryptamines, carbolines and LSD, apparently produce stimulus effects similar to those produced by DOM.

B. Relationships between the Results of Drug Discrimination Studies and Human Hallucinogenic Activity

A number of investigators have commented on the possible inadequacy of animal testing procedures in evaluating hallucinogenic agents. The reasoning behind this opinion is that a subhuman species is unable to adequately communicate the effects of one drug state versus another drug state. However, in the drug discrimination paradigm the animal's behavioral responses are dependent upon the ability of the organism to

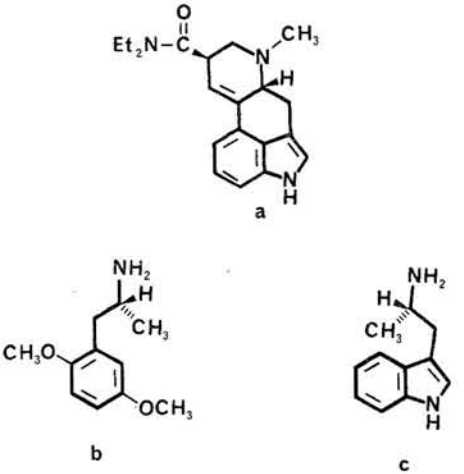


Figure 6. Structural relationship between (a) LSD, (b) *R*(−)-2,5-DMA and (c) *S*(+)-α-methyltryptamine.

detect a specific drug state. Furthermore, generalization studies can be viewed as analogous to administration of a drug to a human subject and then asking the subject to compare the effects of that drug with the effects produced by some standard agent (e.g., LSD, mescaline), with which the subject is familiar.

1. Correlation Studies

Early attempts to correlate the results of generalization studies (ED_{50} values), using 5-OMe DMT as the training drug, with human hallucinogenic potency were only moderately successful (see Fig. 5). However, there is a significant ($r = 0.964$) correlation between the ED_{50} values of 14 phenylisopropylamines and their total human hallucinogenic dose.[36] Although it is not being suggested that the use of the discriminative stimulus paradigm, with DOM (1.0 mg/kg) as the training drug, serves as a model or predictor of human hallucinogenic potency, there certainly exists a relationship between human hallucinogenic potency and discrimination-derived data. To further challenge this relationship, ED_{50} values were determined for several additional agents and Figure 7 shows a plot of log 1/total human hallucinogenic dose (μmoles) vs log $1/ED_{50}$ (μmoles/kg) for the extended series of compounds. DOM-stimulus generalization was not observed for two compounds for which human data exist: PMA and DOAM. PMA, while active in man, may possess an amphetamine-like stimulant component to its overall behavioral actions. Indeed, Martin et al.[89] have reported that PMA produces some behavioral effects which resemble LSD, while other aspects of its pharmacological profile are most similar to amphetamine. DOAM has been the object of only limited human study; Shulgin[38] has stated that a qualitative

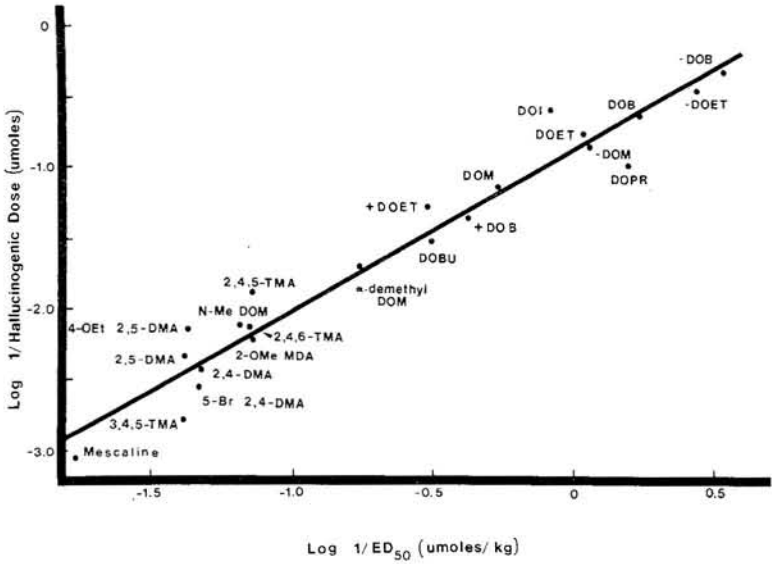


Figure 7. Relationship between the human hallucinogenic potencies of 22 phenalkylamine derivatives and their discrimination-derived ED_{50} values obtained using rats trained to discriminate 1.0 mg/kg of DOM from saline.

description of the syndrome produced by DOAM is unavailable because of the lack of sufficient human evaluation. Based on the drug discrimination assay, it appears that the effects produced by PMA and DOAM differ from those produced by 1.0 mg/kg of racemic DOM.

A significant correlation was also found between human and drug-discrimination data for indolealkylamines (Fig. 8). Included in this figure are two *N,N*-dimethyltryptamines, two α-methyltryptamines, an *N,N*-diisopropyltryptamine, LSD and 6-methoxyharmalan; DOM is also included to show its activity relative to those of the indolealkylamines.

Each of the agents shown in Figures 7 and 8 may not necessarily produce identical hallucinogenic effects in man; each structural (Fig. 9) subclass and, indeed, even certain individual members within a particular subclass, may be characterized by distinctive behavioral subtleties or nuances. Certain agents may even produce various side effects that allow detection of minor differences in their overall human effects. Nevertheless, on the basis of their stimulus properties, all of the agents in Figures 7 and 8 apparently produce similar qualitative effects in rats. Whether rats are more sensitive to the effects that are common to these agents, or whether they lack the repetoire of human behavioral experiences necessary to detect the subtle differences, they are able to both qualitate and quantitate the activities of these agents such that the results parallel those obtained from human studies.[84]

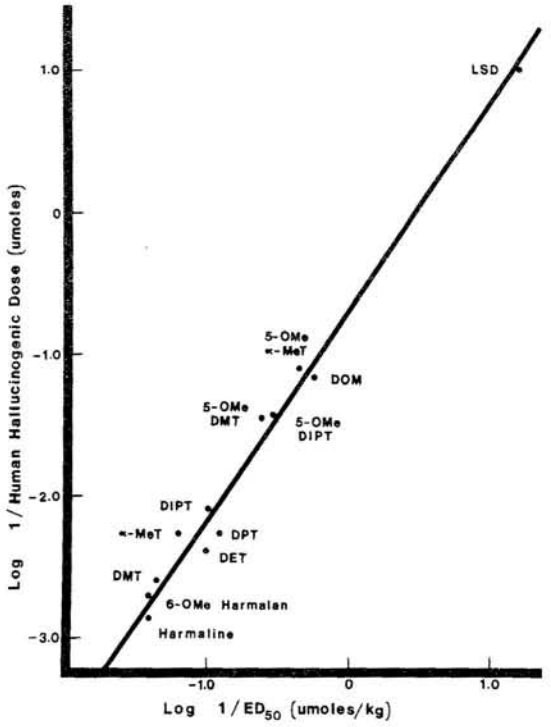


Figure 8. Relationship between the human hallucinogenic potencies of 11 indolealkylamine derivatives and their discrimination-derived ED_{50} values obtained using rats trained to discriminate 1.0 mg/kg of DOM from saline.

2. Speculations with regard to hallucinogenic activity

Members of several classes of hallucinogenic agents are capable of producing common stimulus properties; thus, it might be inferred that these agents (e.g., Fig. 9) produce a common DOM-like effect in rats. Because the quantitative relationships, comparing human data with drug discrimination (i.e., generalization) data, are also similar, it might be assumed that the results of DOM-stimulus generalization in rats may reflect the human situation. Under this assumption, several speculations are possible regarding hallucinogenic activity. First, the receptor system(s) involved in the production of hallucinogenic activity must accommodate all of the structural types involved, if activity is the result of direct receptor interaction. Second, it should be possible to speculate with regard to activity; the remainder of this subsection will deal with this topic. Within the bounds of the potency and activity of the two known hallucinogens mescaline and LSD, several agents, to which the DOM-stimulus generalizes, have been found to be inactive, or have not been evaluated in man. For example, 2,3,4-TMA, 2,3,5-TMA and 5-OEt 2,4-DMA have been found to be inactive in man at doses of up to 100, 50,

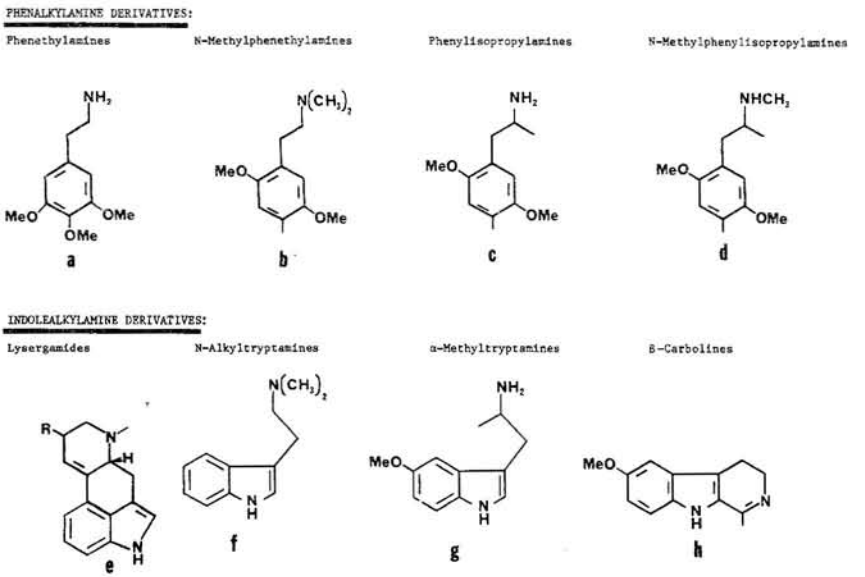


Figure 9. Structural relationships of various phenalkylamine and indolealkylamine derivatives that produce stimulus effects similar to those of DOM: (a) mescaline, (b) *N*,*N*-dimethyl-*N*-demethyl DOM, (c) DOM, (d) N-methyl DOM, (e) LSD, (f) DMT, (g) 5-methoxy-α-MeT, and (h) 6-methoxyharmalan.

and 30 mg, respectively.[38] If these compounds are indeed active, activity should not be observed until doses several times those already evaluated have been administered. *N*-Methylmescaline and *N*,*N*-dimethylmescaline are considered relatively inert in man. *N*-Methylation of several phenalkylamines results in at least a two- to threefold decrease in potency in the discrimination studies; thus, it would be anticipated that the *N*-methyl derivatives of mescaline would not be active in man until doses of at least 900–1500 mg have been administered. Unfortunately, *N*-methylmescaline was only evaluated to 25 mg[38]; *N*,*N*-dimethylmescaline was inactive at 550 mg, although, interestingly, some activity was observed at 800 mg.[38] Note that in mescaline-trained animals, *N*,*N*-dimethylmescaline was approximately half as active as mescaline.[42]

MDA produces both LSD-like and amphetamine-like effects in man, as well as in various animal species. Evidence suggests that *R*(−)-MDA is the hallucinogenic isomer, while *S*(+)-MDA is largely responsible for the stimulant component of activity.[90] Not unexpectedly then, DOM-stimulus generalization occurs with the *R*(−)- but not the *S*(+)-isomer of MDA.[82] Consistent with the above findings, *N*-methylation reduces the hallucinogenic activity of MDA. *N*-Methylation of the nonhallucinogenic phenylisopropylamine amphetamine has little effect on, or actually enhances its CNS-stimulant activity. Thus, in the case of MDA, *N*-methylation appears to reduce the hallucinogenic component while

unveiling the amphetamine component of this agent. This is supported by the finding that *N*-methyl MDA or MDMA produces effects that are distinguishable from those of MDA both in the discrimination study (Table VII) and in man (Shulgin, personal communication), and that *S*(+)-MDMA is more potent than *R*(−)-MDMA.[91]

In general, the *R*(−)-isomers of hallucinogenic phenylisopropylamines are more potent in man than their racemates.[38] The results shown in Table VII support this generality and suggest that *R*(−)-2,5-DMA and *R*(−)-DOI, isomers not yet evaluated in man, should also be more active than their racemates. Isomers of α-methyltryptamines have not been studied in man, however, based on the results of drug discrimination studies, greater hallucinogenic activity should reside in the *S*(+)-isomers of α-methyltryptamine and 5-methoxy-α-methyltryptamine than with their enantiomers.

New compounds such as DOF and DON are relatively active in the discrimination study, while the positional isomers of DOM and DOB (i.e., 3-Me 2,5-DMA, and 3-Br 2,5-DMA) are relatively inactive. It will be interesting, and indeed quite informative, if human data ever become available for any of these agents.

3. *Relevance of the Hallucinogen-induced Cue to Human Drug Abuse*

One of the major difficulties associated with studying problems in the drug abuse area concerns the relevance of the pharmacological procedure employed in experimental animal subjects. The drug discrimination approach has additional credibility over other pharmacological methods in that it is more reflective of the human drug abuser. That is, as with the human subject, the rat in the drug discrimination study is, in effect, a chronic abuser who has had considerable experience with a particular training drug. As such, this animal, like the experienced drug user, might be more sensitive than a naive subject to the effects of related agents, or agents possessing only minimal activity.

C. Use of Drug Discrimination to Study the Mechanism of Action of Hallucinogenic Agents

1. *Studies with Serotonin Agonists*

Serotonin (5-HT) depletion, by, for example, pretreatment with the tryptophan hydroxylase inhibitor PCPA, produces a supersensitivity to LSD in LSD-trained animals,[49,59] and to mescaline in mescaline-trained animals.[48] Apparently, depletion of serotonin does not induce behavioral supersensitivity per se; the pattern, rather than the amount of depletion, seems to be responsible for the observed effects.[59] Rosecrans and co-workers have found that low-current electrical stimulation of the dorsal raphe nucleus, a brain region known to be rich in serotonin neurons, serves as a discriminative stimulus in rats, and that generalization occurs

upon administration of LSD.[92] Furthermore, in rats trained to discriminate LSD (0.12 mg/kg) from saline, LSD administered via chronic indwelling cannula, stereotoxically implanted in the area of the raphe, elicited greater than 80% LSD-appropriate responding.[60] Correlations exist between the ability of a 5-OMe DMT stimulus to generalize to a series of indolealkylamine and phenalkylamine derivatives and their rat fundus serotonin receptor affinities.[70] Similar findings have been reported using DOM as the training drug.[36] Agents such as LSD, 5-OMe DMT, 5-OMe DET, and 5-OMe DPT have been demonstrated to possess high affinities for rat brain 5-HT_1 binding sites.[93,94] Based on these and other (see discussion on antagonism studies) findings, it is not unusual to suspect that serotonin might play at least a partial role in the stimulus effects produced by mescaline, LSD, 5-OMe DMT, and DOM.

Quipazine, i.e., 2-(1-piperazinyl)-quinoline, maleate is a purported serotonin agonist, which has been demonstrated to displace tritiated serotonin binding to rat brain membranes with an IC_{50} in the 400–700 n*M* range.[94,95] When administered to rats trained to discriminate LSD from saline, quipazine produced LSD-appropriate responding.[52,53,55] Quipazine has also been found to produce DOM-appropriate responding (Glennon et al., unpublished observation), while administration of quipazine to mescaline-trained animals resulted in a maximum of 58% mescaline-appropriate responding.[55] Quipazine produced 48% and 71% correct drug-lever responding in animals trained to discriminate 3.0 mg/kg and 1.0 mg/kg, respectively, of 5-OMe DMT from saline, suggesting training-dose-related effects (unpublished data). In rats trained to discriminate LSD from lisuride, administration of apomorphine produced lisuride responding, while quipazine elicited LSD-appropriate responding.[61] In more recent studies, quipazine itself has been used as a training drug in tests of discriminative stimulus control of behavior.[54,55,96] Based on their studies, White et al.[96] have concluded that quipazine might possess hallucinogenic properties. Indeed, it has been reported that 0.5 mg of quipazine produces low-dose mescaline-like effects in man (personal communication cited by Winter[55]), however, detailed clinical studies confirming this activity have never been published.

Three other potential serotonin agonists have been briefly examined: MK-212, i.e., 6-chloro-2-(1-piperazinyl)-pyrazine; TFMPP, i.e., 1-(3-trifluoromethylphenyl)-piperazine; and RU-24969, i.e., 5-methoxy-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1H-indole (see Fig. 10). Brain binding studies have revealed that each of these agents is capable of displacing tritiated serotonin; their approximate nanomolar IC_{50} values are 15,000,[97] 200,[95] and 7,[93] respectively. Like quipazine, administration of MK-212 to rats trained to discriminate LSD (0.02, 0.08, and 0.32 mg/kg) from saline resulted in LSD-stimulus generalization; MK-212 was approximately twice as potent as quipazine in this regard.[35] Unlike quipazine, however, neither TFMPP nor RU-24969 produced DOM-appropriate responding

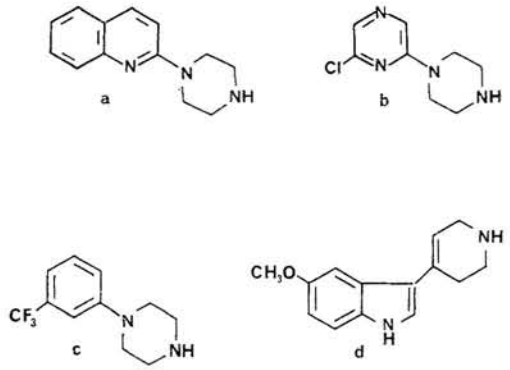


Figure 10. Structures of four purported 5-HT agonists: (a) quipazine, (b) MK-212, (c) TFMPP, and (d) RU-24969.

(Glennon et al., unpublished observations). It appears, based on these preliminary results, that a direct relationship does not exist between the ability of LSD and/or DOM to generalize to quipazine, MK-212, TFMPP, and RU-24969 and their ability to displace tritiated serotonin from rat brain membranes. However, recent evidence suggests (a) that quipazine, unlike TFMPP, might produce considerable presynaptic, as well as postsynaptic, effects[98]; (b) that RU-24969 might interact with sites other than serotonin binding sites, as noted by its Hill coefficient[93]; and (c) that TFMPP interacts differentially with 5-$HT_{1\text{-}A}$ and 5-$HT_{1\text{-}B}$ sites. Thus, too little is currently known about these serotonin agonists, and too few discrimination studies have been conducted employing these agents, to draw any definitive conclusions at this time.

2. *Studies with Serotonin Antagonists*

The ability to determine the mechanism of action of any agonist is, in part, contingent upon the development of specific antagonists. In the case of the hallucinogenic drugs the availability of selective antagonists has been lacking and progress in the development of such agents has been slow. Because of evidence suggesting that LSD, and drugs producing subjective effects similar to those of LSD, may be producing their effects by an interaction at 5-HT neurons, much research has focused on the ability of purported 5-HT antagonists to inhibit a variety of hallucinogenic cues (Table IX). The overall results of these studies do support a 5-HT hypothesis of hallucinogenic action.

In addition to studying 5-HT antagonist interactions, attempts to block the hallucinogen-elicited cue by a variety of other pharmacological antagonists such as naloxone, atropine, haloperidol, or various phenothiazines has also been made, but with little success.[49,52] The possible involvement of the 5-HT neuron has led several investigators to attempt to modify the discriminative stimulus properties of these drugs by

Table IX
Attenuation of Various Hallucinogen-Induced Discriminative Stimulus Cues by Purported 5-HT Antagonists

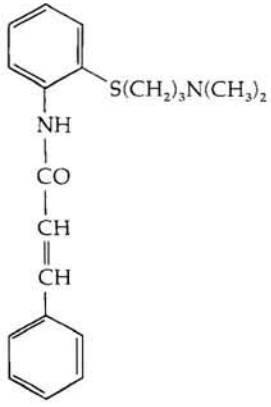
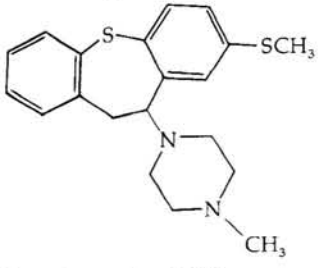
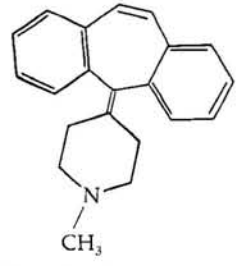
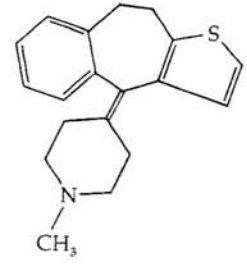
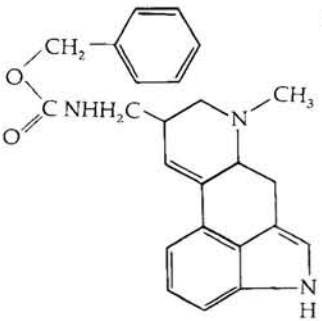
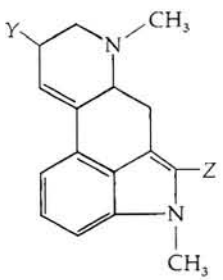
Antagonist	Agonist Cue	% Inhibition[a]	Reference
Cinanserin (CIN) 	Mescaline	66%	Browne and Ho[48]
	Mescaline	(95%)	Winter[44]
	Mescaline[b]	89%	Silverman and Ho[46]
	Mescaline[c]	77%	Minnema[e,110]
	DOM	96%	Silverman and Ho[33]
	DOM[d]	78%	Winter[44]
	DOET[b]	95%	Silverman and Ho[33]
	Quipazine	77%	Minnema[e,110]
	Psilocybin[b]	97%	Silverman and Ho[33]
	LSD[b]	86%	Silverman and Ho[33]
	LSD	32%	Minnema[e,110]
	LSD	45%	Kuhn et al.[52]
	LSD	(60%)	Colpaert et al.[62]
	5-OMe DMT	39%	Young et al.[f,101]
Methiothepin (MTP) 	Mescaline[c]	66%	Minnema[e,110]
	Quipazine[c]	46%	Minnema[e,110]
	Quipazine	(70%)	White et al.[103]
	LSD	(70%)	Kuhn et al.[52]
	LSD	39%	Rosecrans et al.[102]
	LSD	7%	Minnema[e,110]
	5-OMe DMT	32%	Young et al.[101]
	5-OMe DMT	16%	Rosecrans et al.[102]
Cyproheptadine (CYP) 	Mescaline	55%	Browne and Ho[48]
	Mescaline[c]	86%	Minnema[e,110]
	Quipazine	(70%)	White et al.[103]
	Quipazine[c]	83%	Minnema[e,110]
	LSD	(70%)	Kuhn et al.[52]
	LSD	(40%)	Colpaert et al.[62]
	LSD	82%	Minnema[e,110]
	5-OMe DMT	84%	Young et al.[f,101]
Pizotifen (BC-105) 	Mescaline	(95%)	Winter[44]
	Mescaline[c]	98%	Minnema[e,110]
	DOET[d]	81%	Winter[44]
	LSD[d]	79%	Winter[44]
	LSD	90%	Rosecrans and Glennon[54]
	LSD	92%	Minnema[e,110]
	LSD	(70%)	Colpaert et al.[62]
	Quipazine[c]	91%	Winter[44]
	5-OMe DMT	84%	Glennon et al.[16]
	DOM	99%	Young et al.[12]

Table IX
Continued

Methergoline (MCE) 	LSD	(40%)	Colpaert et al.[62]
	5-OMe DMT	32%	Young et al.[f,101]
Methysergide (UML)[g]	Mescaline	42%	Browne and Ho[48]
	Quipazine	(25%)	White et al.[103]
Y = CH(OH)NHCH—CH_2OH	LSD	(70%)	Kuhn et al.[52]
CH_2CH_3	LSD	32%	Minnema[e,110]
Z = H	LSD	(25%)	Colpaert et al.[62]
	5-OMe DMT	15%	Young et al.[f,101]
	DOM	89%	Silverman and Ho[33]
2-Bromo LSD (BOL)[g]	Quipazine	(30%)	White et al.[103]
Y = $CON(C_2H_5)_2$	LSD	(30%)	Kuhn et al.[52]
Z = Br	LSD	(40%)	Colpaert et al.[62]

[a]Percent inhibition of drug-appropriate responding by a given antagonist was calculated from numerical data provided in tabular form from the cited reference, or, for those values given in parenthesis, was approximated from graphical data.
[b]Antagonism study involved stimulus generalization using animals trained to discriminate DOM from saline.
[c]Antagonism study involved stimulus generalization using animals trained to discriminate LSD from saline.
[d]Antagonism study involved stimulus generalization using animals trained to discriminate mescaline from saline.
[e]Unpublished data from a doctoral thesis; see Table X.
[f]Some of these data obtained from values shown in Table X.
[g]See general structure below:



manipulating 5-HT synthesis or reuptake mechanisms, but, again with little success. The results of these approaches suggest that presynaptic 5-HT is not necessary for the generation of hallucinogen-elicited stimulus effects, and that the cue doesn't seem to involve either cholinergic, narcotic, or catecholamine receptors. Thus, the body of data at this time does seem to point to some postsynaptic 5-HT receptor as necessary for an animal to be able to discriminate the hallucinogens from saline.

a. Results of antagonism experiments. What follows is a discussion of specific studies directed toward evaluating the role of 5-HT using the drug antagonist approach. Hopefully, some of the apparent confusion engendered by these experiments will be clarified.

(i) Cinanserin (CIN). Since the initial studies describing the stimulus properties of hallucinogens, many attempts have been made to identify antagonists that might specifically and selectively block these stimulus cues in a competitive manner. However, it wasn't until 1975 that it was shown that a hallucinogen cue could be attenuated by a purported 5-HT antagonist (see Table IX). Browne and Ho demonstrated that cinanserin (CIN), cyproheptadine, (CYP) and methysergide (UML) were effective antagonists of the mescaline cue.[48] The degree of antagonism was not

Table X
Effect of Several 5-HT Antagonists Administered to Rats Trained to Discriminate either LSD or 5-OMe DMT from Saline.

	% LSD-appropriate responding[b]			% 5-OMe DMT-appropriate responding[c]	
Pretreatment[a]	LSD (0.06 mg/kg)	Quipazine (2.0 mg/kg)	Mescaline (10 mg/kg)	5-OMe DMT (1.5 mg/kg)	5-OMe DMT (3.0 mg/kg)
Saline	93%	88%	95%	93%	95%
BC-105 (1.0)	17%	24%	2%	13%	85%
CYP (2.0–2.5)	16%	15%	13%	14%	89%
CIN (5–15)	65%	12%	20%	55%	89%
MTP (1.0)	87%	48%	34%	—	—
UML (10–15)	50%	—	—	76%	61%
MCE (2.0)	—	—	—	61%	61%

[a] Numbers in parenthesis refer to the doses (mg/kg) employed.
[b] The quipazine and mescaline cues were evaluated in animals trained to discriminate LSD from saline. Data abstracted from a doctoral thesis submitted by D. Minnema.[110]
[c] Groups of rats were trained to discriminate either 1.5 or 3.0 mg/kg of 5-OMe DMT from saline.[101]

complete but CIN did attentuate the cue by 66%. Xylamidine which appears to act at only peripheral 5-HT sites, on the other hand, was ineffective, indicating that the site of the mescaline cue was of central origin. Winter further demonstrated that the mescaline cue could be completely antagonized by both CIN and pizotifen (BC-105), with BC-105 being the more potent.[43,100] The generalization of mescaline to other hallucinogens such as LSD, DOET, and DOM was likewise completely antagonized by CIN and BC-105. Silverman and Ho,[33,46] using DOM-trained animals, provided further evidence of CIN's efficacy as an antagonist of the hallucinogen cue and also demonstrated that this antagonist was effective against generalizations of DOM to DOET, LSD, mescaline, and psilocybin (Table IX). In each case the antagonism was almost complete, with drug-appropriate responses being reduced by 85%.

While cinanserin appeared to be an effective antagonist in both mescaline and DOM-trained rats, its efficacy in LSD-discriminating rats appeared to be somewhat less. Kuhn, et al.,[52] and Minnema (Table IX) observed CIN to reduce the LSD cue by less than 45%, while we have found (unpublished data) CIN to be relatively ineffective in both LSD and 5-OMe DMT-trained animals. Colpaert et al.[62] (Table IX) demonstrated more success with CIN as they observed a 60% antagonism of the LSD cue. However, none of these studies produced the levels of antagonism of LSD similar to those observed when mescaline or DOM were used as training drugs. Success with CIN as an antagonist in our laboratory occurred only in studies involving generalizations of LSD to mescaline and quipazine (Table X); in each case, the antagonism was almost complete.[110]

(ii) Methiothepin (MTP). Kuhn et al.[52] were the first to study MTP as an LSD antagonist in the discrimination model and were able to attenuate this cue by at least 70%. Research conducted in our laboratories have been unable to replicate these above studies with either 5-OMe DMT or LSD serving as the discriminative stimulus cues.[101,102] We have no explanation as to why these differences should exist except that different schedules of reinforcement were employed on different occasions. Our initial studies utilized a VI-15 schedule and a higher training dose of LSD[102] than did those of Kuhn et al.,[52] who employed an FR-32 schedule of reinforcement. In our most recent study,[110] however, MTP was again ineffective even though an FR-10 schedule and a lower dose of LSD was used (Table X).

(iii) Cyproheptadine (CYP and pizotifen (BC-105). These two agents will be discussed together because of their similar pharmacological and structural characteristics (Table IX). Most investigators have been quite successful in attenuating the hallucinogen cue with these agents (Table IX). Research conducted in our laboratories have shown both drugs to be almost equally potent in attenuating the discriminative stimulus effects of LSD, 5-OMe DMT and DOM.[12,54,63] Similar results were observed in

studies where the LSD cue generalized to either quipazine or mescaline. In this latter study, all three cues (included) were antagonized by these agents (Table X). As already pointed out, several of the antagonists appear less potent against LSD but more effective in antagonizing generalization tests of LSD to either mescaline or quipazine. Colpaert et al.,[62] while reporting BC-105 to be one of the better LSD-antagonists, observed CYP to be less than adequate. However, their study employed a training dose of LSD (0.16 mg/kg) that is higher than that used by most other investigators. In addition, Colpaert et al.[62] reported that several of these antagonists, when administered at sufficiently high doses, also exhibit agonist properties. While Colpaert et al.,[62] observed a significant agonist effect of BC-105, we have not observed an analgous effect at doses ranging between 1.0–3.0 mg/kg (i.e., at doses which block the LSD cue). By itself, BC-105 produces only saline-appropriate responding when administered to rats trained to discriminate either LSD or 5-OMe DMT from saline.[12,16]

(iv) Other antagonists. UML, methergoline (MCE) and 2-bromo-LSD (BOL) appear to be weak antagonists of the LSD and 5-OMe DMT cue (Table IX); only Kuhn *et al.*[52] report antagonism of the LSD cue with UML. A major assumption in drug discrimination research is that stimulus cues generated by drugs such as the hallucinogens are the result of a stimulation of pharmacological and/or physiological receptors located at some central brain area site. To rule out the possibility of some peripheral nervous system involvement, several investigators have attempted to antagonize these drug cues with the peripheral 5-HT antagonist, xylamidine. To date none of the cues studied has been antagonized by this antagonist indicating that the major site of action of these cues is at some central 5-HT receptor site.[35,48,101] However, the dose of the training drug used may have some importance as White and Appel[35] observed xylamidine to antagonize the cue elicited by LSD doses of 0.02 mg/kg (LSD correct responses reduced to $\geqslant 40\%$), but not at doses of 0.08 or 0.16 mg/kg. This suggests that low-dose cues may be more susceptible to antagonism by nonselective or peripherally active antagonists.

b. Problems associated with the use of 5-HT antagonists. In addition to the recent discovery of subpopulations of 5-HT receptors,[99,104–106] there are several other problems associated with the use of 5-HT antagonists in drug discrimination experiments.

(i) Agonist properties of 5-HT antagonists. Because of the apparent competitive nature of the hallucinogen agonist–antagonist relationship at the 5-HT receptor, one might also suspect that these purported 5-HT antagonists to also exhibit agonist properties at some dose. Colpaert et al.[62] tested this possibility in rats trained to discriminate high doses of LSD (0.16 mg/kg). Several of these agents were found to exhibit LSD-correct responding when given alone, but these effects were observable

only at extremely high doses. For example BC-105 produced a minimal agonist effect at 40 mg/kg, which is 40 times the dose needed to completely antagonize either the LSD or 5-OMe DMT cue.[63] Methylsergide and cyproheptadine, however, did produce agonist effects at lower doses than that of BC-105. In these studies, methylsergide was clearly a partial agonist, in fact it appeared to be more of an agonist. A similar effect was noted by Hirschhorn and Rosecrans.[14]

While we believe that these agents have some agonist properties, these effects are observable only at high doses. However, a comparison of the data obtained by Colpaert et al.[62] and that obtained in this laboratory[101] does indicate that of the antagonists studied, BC-105 is the most specific and selective.

(ii) Degree of antagonism vs training dose. Research involving 5-HT antagonists to explore the mechanism of action of hallucinogenic agents and to define the mechanisms underlying the stimulus properties of drugs, while at times confusing, should be viewed, retrospectively, as the development of a new area. It has taken some time to learn how to study these agonists and antagonists. As recently shown by White and Appel[35] the sensitivity of the discriminative stimulus cue, and the ability to antagonize it, are greatly affected by dose. It is incorrect to assume that hallucinogens such as LSD or 5-OMe DMT are exerting stimulus control of behavior by interacting at 5-HT receptors at all training doses. Experiments conducted in this laboratory indicate that 5-OMe DMT may be acting at some 5-HT receptor at a training dose of 1.5 mg/kg (Table X), but that its mechanism of action may be somewhat different at a training dose of 3.0 mg/kg. Neither BC-105 nor CYP were effective in antagonizing the 3.0 mg/kg dose of 5-OMe DMT suggesting that this agonist may be acting at a different set of 5-HT neurons not accessible to the antagonists; or alternatively, that 5-OMe DMT is acting at some non-5-HT sensitive receptor site. These data are even more intriguing since the high training dose (3.0 mg/kg) of 5-OMe DMT does generalize to LSD at 0.06 mg/kg (86% 5-OMe DMT-appropriate responding, a dose of which in LSD-trained animals, is completely antagonized by BC-105.[101] However, the generalization of 5-OMe DMT to LSD at 0.18 mg/kg (100% 5-OMe DMT-appropriate responding) was not antagonized by BC-105 (1.0–9.0 mg/kg) suggesting that mediation of each of these cues, at the higher doses, are quite similar.

The lesson to be learned is that one needs to study drug cues at several training doses in the presence of different doses of antagonist to obtain a better understanding of the drug-receptor interactions. Young et al.[63] (Fig. 11) compared LSD and 5-OMe DMT dose-response curves in the presence of different doses of BC-105 and noted some differences on the effects of these drugs. The data did not alter our hypothesis that these discriminative stimulus cues are generated by an overall 5-HT receptor interaction, however, the shape of the resulting dose-response curves do

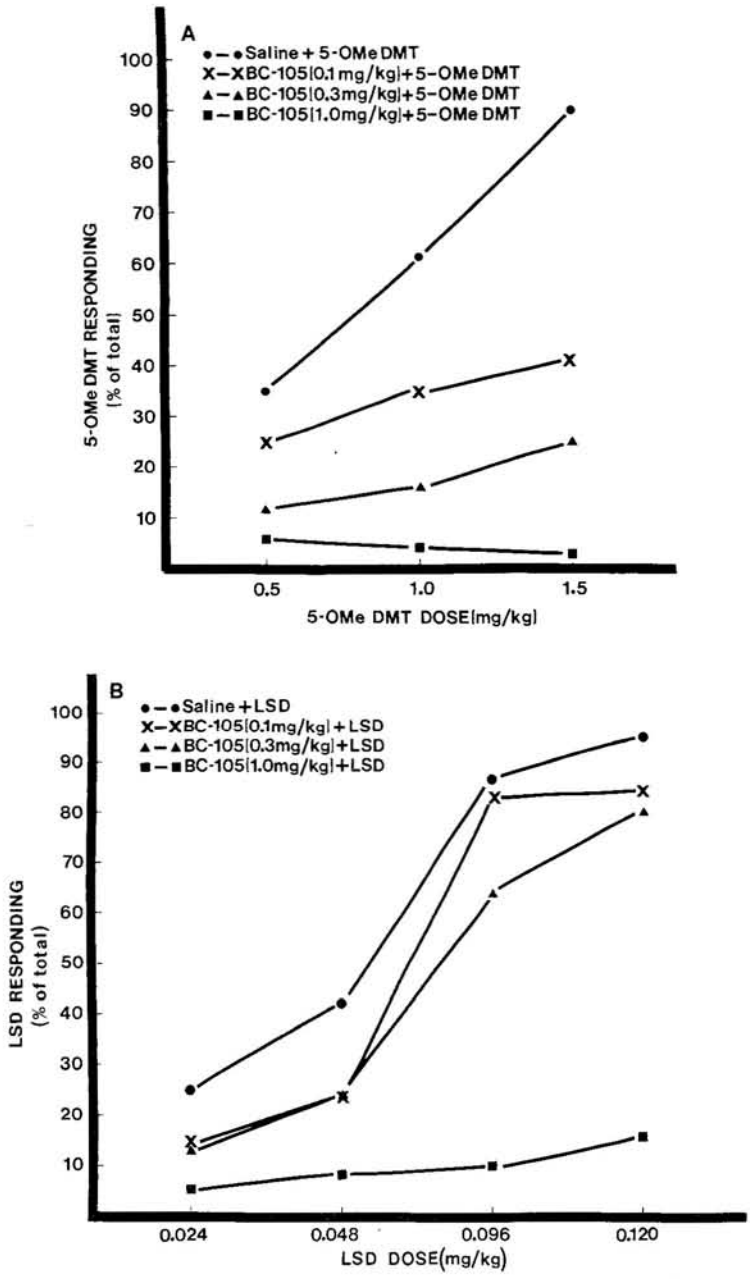


Figure 11. Dose-response curves to 5-OMe DMT (A) and LSD (B) in the presence of several doses of the 5-HT antagonist BC-105, in animals trained to discriminate 1.5 mg/kg of 5-OMe DMT from saline.

suggest that the nature of the agonist–receptor interaction may be different for each compound.

(iii) Lack of specificity. Another difficulty in working with 5-HT antagonists is that the antagonists studied to date lack specificity. Most of these agents tend to have an effect on other receptor ligands such as, for example, histamine.[107] In a study conducted in these laboratories,[108] using rats trained to discriminate BC-105 (6 mg/kg) from saline, complete stimulus generalization occurred with only one 5-HT antagonist, CYP; this is reasonable because of the close structural and pharmacological similarity of these two compounds. Interestingly, the BC-105-stimulus generalized to the tricyclic antihistamine promethazine (PMZ), but not to diphenhydramine. This suggests that BC-105, at least at high doses, may induce stimulus control by its antihistamine properties. PMZ did not antagonize the LSD cue providing further support for the conclusion that the ability of BC-105 (at 1 mg/kg or less) to antagonize LSD is via a 5-HT interaction, and most likely does not involve histaminergic receptors. Finally, the finding that BC-105 (1.0–9.0 mg/kg) was unable to antagonize high doses of either 5-OMe DMT (3.0 mg/kg) or LSD (0.18 mg/kg in 5-OMe DMT-trained rats) suggests that histamine receptors were not involved in these cues. Thus, one must be very cautious in any conclusions drawn with these agents.

3. *Studies with LSD Antagonists*

As evident from the discussion at the outset of the section on 5-HT antagonists, none of the available antagonists fulfill all the necessary requirements. Some of these agents possess 5-HT agonist properties (e.g., methysergide), while others may disrupt behavior because of possible neuroleptic properties (e.g., methiothepin). BC-105, which apparently is quite specific and which produces little effect of its own on behavior, appears to possess antihistamine properties at six times its LSD-antagonist dose,[107,108] and exhibits 5-HT agonist effects at 40 times its antagonist dose.[62] Recently, Colpaert et al.[62] have reported on the activity of pirenpirone (Fig. 12), an extremely potent LSD antagonist. Pirenpirone displays activity as an LSD antagonist at subcutaneous doses of as little as 0.01 mg/kg in rats; a dose of 0.16 mg/kg of pirenpirone will completely block the effects of 0.16 mg/kg of LSD in LSD-trained rats. By itself, it produces relatively little behavioral disruption, and does not appear to produce agonistic effects. Appel et al.[109] have observed similar effects for pirenpirone in rats trained to discriminate either 0.08 or 0.16 mg/kg of LSD from saline. In our own laboratories, we have found that pirenpirone completely blocks the effects of 1.0 mg/kg of DOM in DOM-trained animals, and that it also blocks generalization of the DOM stimulus to LSD, 5-OMe DMT, and mescaline (unpublished data). With respect to potency, pirenpirone is approximately 25 times more active than BC-105.

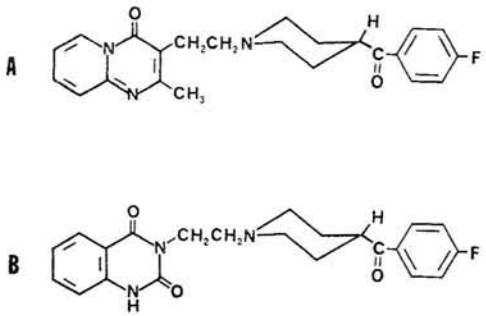


Figure 12. Structures of two 5-HT_2 antagonists: (A) pirenpirone and (B) ketanserin.

Interestingly, Leysen et al. have demonstrated that pirenpirone binds to brain membrane 5-HT_2 sites ($-\log IC_{50} = 9.03M$) with a greater affinity than it has for 5-HT_1 sites.[111] These data seem to suggest a potential role for 5-HT_2 in the mechanism underlying the stimulus cues of certain hallucinogens. However, ketanserin (Fig. 10), which also binds selectively to 5-HT_2 sites ($-\log IC_{50} = 8.88M$),[111,112] has been found, in preliminary studies, to be about 10–30 times less active than pirenpirone in blocking the LSD cue, or the DOM cue.[109] Nevertheless, these results offer new leads that may eventually lead to a better understanding of the role of 5-HT in the mechanism of action of hallucinogenic agents.

D. Other Approaches to Studying Mechanisms of Hallucinogenic Drug Action

This review has primarily focused on SAR and on antagonism approaches to studying the mechanisms underlying the stimulus properties of hallucinogens. While these studies have been extremely useful towards an understanding of the nature of the receptor interaction needed for the generation of such cues, we have little information relative to specific brain area sites of action. Several additional experimental approaches can be utilized for such studies.

Most of the work directed toward identifying the sites of action of hallucinogens have centered on specific neurophysiological methods especially via the iontophoretic application of hallucinogens to various brain sites (for example, see ref. 113). While such research can be quite instructive, it doesn't get to the heart of the issue of attempting to correlate site of action with *in vivo* drug effect. The drug discrimination approach, as already demonstrated, is specific and sensitive within a pharmacological class of drugs, and appears to measure pharmacological effects which clearly parallel those effects described in man (Fig. 6). Thus, we have a unique opportunity of using a very specific pharmacological technique to study sites of drug action as discriminative stimuli, with implications for the mechanism of action of hallucinogens in humans.

Several approaches have already been used, and primarily involve the manipulation of 5-HT systems in order to search out some underlying site of action. Depletion of the 5-HT system by using neurotoxins such as 5,7-dihydroxytryptamine administered neonatally have been studied.[110] Unfortunately, the results of these studies have provided relatively little new data except that research involving a destruction of dopamine systems suggest that this system may have some inhibitory effects on 5-HT receptors, resulting in an increased sensitivity to the LSD cue. The overall thrust of this research has pointed to the postsynaptic 5-HT receptor as a major site of action for LSD, as rats are able to discriminate LSD regardless of the presence of presynaptic 5-HT.

Other more physiological approaches involve an attempt to mimic the LSD cue by either the electrical stimulation or the application of drug and/or receptor ligands at suspected sites along various segments of these 5-HT pathways. This approach has not yet been evaluated completely and only two studies have been reported.[60,92] In the first study, Hirschhorn et al.[60] observed that rats trained to discriminate electrical stimulation of the midbrain raphe (5-HT is presumed to be released at rostral sites in the forebrain) generalized to doses of LSD (0.06–0.08 mg/kg) used in our drug discrimination research. In the second, LSD (0.096 mg/kg, i.p.) trained rats generalized to doses of LSD (0.02 mg) administered directly into the raphe nucleus. While both studies provide support for a 5-HT cell body (raphe nucleus) site for LSD,[92] the technical difficulties encountered cause us to be very cautious as to our final conclusions. However, we encourage more investigators to use these approaches because it is these that will most likely yield the most useful information concerning specific sites and mechanisms of action of hallucinogenic drugs. In fact, the incorporation of such neuropharmacological methodologies with the agonists and antagonists described here could provide an exquisite picture of how such discriminative stimulus cues are generated.

IV. Conclusion

The drug discrimination paradigm is a very powerful pharmacological procedure which should prove to be quite useful for studying the effects of CNS-active agents. It has been shown that a number of such agents serve as discriminative stimuli, and that stimulus properties are both time and dose dependent. Although tolerance develops to the disruptive effects of various training drugs, it does not appear to develop to their behavioral effects (i.e., stimulus cueing properties). Stimulus generalization between a training drug and a challenge drug is evidence that both agents are capable of producing similar stimulus effects, although not necessarily via the same mechanism of action. Thus, using this procedure, it should be possible to examine a series of agents and to identify those members of the series that produce stimulus effects similar to those of a particular training drug. In essence, the drug discrimination

paradigm can be used to evaluate the effects of novel agents and/or to investigate their SAR. It should be emphasized, at this point, that evaluations of the stimulus properties of a novel agent should not substitute for, nor does it constitute, a thorough pharmacological study of that agent. Nevertheless, this procedure can serve as a very convenient method for examining the activity and duration of action of a novel agent, as well as the activity of potential metabolites, optical isomers, and related molecular modifications. Like many other *in vivo* pharmacological models/methods, the drug discrimination method will reflect the overall consequences of a particular agent including its absorption, distribution, and metabolic characteristics. Thus, SAR formulated from discrimination data may not necessarily parallel SAR derived from various *in vitro* studies.

Mechanism of action can be investigated from several standpoints. For example, generalization experiments can be performed using known agonists as challenge drugs, or specific antagonists can be administered in attempts to attenuate the effects of a training drug. (Conversely, this procedure can also be used to identify new potential agonists and antagonists.) Useful results may also be obtained by employing other neurochemical and neurophysiological manipulations.

As an example of the application of the drug discrimination paradigm, a review of its use in studying several classes of hallucinogenic agents has been included. Many of the approaches mentioned above have been applied to these agents, and sample results have been presented. The usefulness of this approach is readily apparent. The same may be said of its shortcomings (i.e., the nature of the discriminative stimulus cue is not fully understood). Nonetheless, results generated from discrimination studies are, in general, consistent with the results of previous pharmacological studies, and have advanced our knowledge with respect to the structure–activity relationships and the mechanism of action of hallucinogenic agents.

Much of the work (from our laboratories) described herein was supported by U.S.P.H.S. grant DA-01642 (to R.A.G.).

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