Classical Hallucinogens: An Introductory Overview

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INTRODUCTION

Classical hallucinogens may be broadly divided into two categories: indolylalkylamines and phenylalkylamines. The indolylalkylamines may be further divided into:

- simple tryptamines (e.g., N,N-dimethyltryptamine [DMT], 5-methoxy DMT, psilocin);
- α-methyltryptamines (e.g., a-MeT, 5-methoxy a-MeT);
- ergolines (e.g., (+)lysergic acid diethylamide [(+)LSD]); and
- ß-carbolines (e.g., harmala alkaloids).

Phenylalkylamines may be subdivided into:

- phenylethylamines (e.g., mescaline) and
- l phenylisopropylamines (e.g., 1-(2,5-dimethoxy-4X-phenyl)-2-aminopropanes where X = methyl, bromo, or iodo (i.e., DOM, DOB, and DOI, respectively).

For general reviews, see Nichols and Glennon (1984).

What constitutes a hallucinogenic agent? There have been various attempts to define the term "hallucinogenic," but none of the definitions seems to adequately, accurately, and completely describe the actions of these agents. Perhaps one of the better definitions-actually, a set of criteria-is that provided by Hollister (1968): (1) in proportion to other effects, changes in thought, perception, and mood should predominate; (2) intellectual or memory impairment should be minimal; (3) stupor, narcosis, or excessive stimulation should not be an integral effect; (4) autonomic nervous system side effects should be minimal; and (5) addictive craving should be absent.

It is recognized that not all classical hallucinogens necessarily produce identical effects. In fact, it has been said that a dose of a given agent may produce different effects in the same individual upon different occasions

of administration (Naranjo 1973), and that the human subject is as much a contributor to the final definition of a drug's action as is the drug itself (Shulgin and Shulgin 1991). Clearly, there exist some differences in effect. How can these differences be rationalized? There are several likely explanations: (1) effects may be dose-dependent (and additional examination of more doses of more agents in more subjects may reveal greater similarity than difference); (2) side effects may contribute substantially to the observed differences; (3) the agents may not constitute a mechanistically homogeneous group of compounds; and/or (4) the classical hallucinogens may act via similar but nonidentical mechanisms that share a common mechanistic component.

Because there is some evidence for similarity of effect, the last explanation (the common component hypothesis) provides a framework for mechanistic investigations. That is, the effects produced by hallucinogens may be likened to response patterns formed by certain neurohumoral "keys" played on a piano with the resulting chords being manifested as differently perceived behavioral effects (Glennon 1984). Identification of a common key may be important to further understanding of these agents. Agents lacking a common component are likely acting via a different mechanism; such agents may need to be categorized separately, and such categorization may influence future treatment modalities.

HALLUCINOGENIC AGENTS: METHODS OF INVESTIGATION

Hallucinogenic agents have been investigated using both human and nonhuman subjects. Obviously, only human subjects possess the faculties required to accurately assess and describe the subjective effects of these agents. However, relatively few hallucinogens have been examined in humans (however, see Shulgin and Shulgin 1991), and legal constraints discourage new clinical studies. Investigations involving nonhuman subjects are much more common, allow the examination of greater numbers of agents in large numbers of subjects, and are certainly less restrictive in terms of governmental regulation. However, there are obvious limitations to this approach, the most prominent being that it is not known if animals experience subjective effects identical to those experienced by humans. On the other hand, lacking the sophisticated behavioral repertoire of humans, animals may (?) be better able to focus on the common effects produced by these agents.

Animal studies tend to fall into two categories: investigative (i.e., observational) and interpretive. The former simply categorizes the effects of known hallucinogens in animal subjects (e.g., effect on electroencephalographic patterns, social behavior, and sleep cycles) in an attempt to catalog their pharmacological effects without further interpretation. The latter addresses possible mechanisms involved in the production of these effects. Mechanistic interpretation must necessarily be conservative, and identified mechanisms may or may not be related to the hallucinogenic activity of the agents under investigation.

Another type of investigation involving animals is the development of animal models to identify novel hallucinogens. Such studies begin with examination of known hallucinogens to determine what effects are common to a series of agents but absent upon administration of inactive agents. Once such an effect has been identified, the model ideally is challenged with other hallucinogens and nonhallucinogens and ultimately with novel agents. It never can be assured that novel agents identified in this manner will be hallucinogenic until they have been evaluated in human subjects. Nevertheless, robust and reliable animal models can be valuable for further mechanistic investigations by allowing experimentation not appropriate (or allowed) in humans. Here also, greater numbers and doses of agents can be evaluated in relatively large subject populations.

Thus, studies involving human and nonhuman subjects have their own peculiar limitations, advantages, and disadvantages. The ideal situation likely would be investigations involving both types of subjects.

MODELS OF HALLUCINOGENIC ACTIVITY

Animal Models

Over the years there have been numerous reports of animal models that might be useful for examining hallucinogenic agents (reviewed: Glennon 1992). Animal models are of two types: behavioral and nonbehavioral. The behavioral models are further divided into analog models and assay models (Stoff et al. 1978); others have referred to these models as "isomorphic models" and "parallel models," respectively (Jacobs and Trulson 1978). Analog models are correlational; that is, they rely on some drug-induced animal behavior for which there is an intrinsic similarity in human effect (e.g., exploratory behavior and stereotypy).

Assay models are inferential; that is, there need not be a relationship between the animal and human behavior so long as the test drugs produce a dose-related effect that parallels human hallucinogenic potency. It has been whimsically suggested that if hallucinogens elicited tail-biting behavior in rodents in a dose-dependent manner with a potency that parallels human hallucinogenic potency, then tail-biting could be a useful assay model of hallucinogenic activity (Stoff et al. 1978).

Nonbehavioral animal models may be of an analog or assay nature but simply rely on effects that are not necessarily behavioral (e.g., contraction of isolated muscle tissue in a muscle bath). Some common explicit or implicit animal models include (1) the serotonin syndrome; (2) ear-scratch reflex or scratch reflex stereotypy; (3) head-twitch response; (4) rabbit hyperthermia; (5) limb-flick behavior in cats or limb-jerk in monkeys; (6) startle reflex; (7) investigatory behavior; (8) disruption of fixed-ratio responding, the so-called hallucinogenic pause; and (9) drug discrimination (DD) using animals trained to standard hallucinogens (reviewed: Glennon 1992). Combinations of these and other assays have been employed as test batteries (Otis et al. 1978; Stoff et al. 1978) with the hope that a combination of tests might prove more reliable. To date, however, there is no foolproof animal model that allows reliable predictions of hallucinogenic activity. That is not to say that the use of animal models is not worthwhile; indeed, they have enhanced the understanding of hallucinogenic agents significantly, Unfortunately, each model has resulted in some false positives (i.e., has identified an agent known to be inactive in humans as being potentially hallucinogenic) and/or false negatives (i.e., has identified a known hallucinogen as being potentially inactive).

Nonanimal Models

Nonanimal techniques have been employed to investigate hallucinogenic agents and, in particular, the structure-activity relationships (SAR) of such agents. These may be classified as stochastic interaction models, conservative molecule models, and mechanistic models (Kier and Glennon 1978). Stochastic interaction models are simulations of drug-receptor interactions in the absence of any understanding of the receptor involved (i.e., the model features interactions between an active drug molecule and some hypothetical receptor feature). The conservative molecule approach is an investigation of the structural influence (e.g., physicochemical or quantum chemical properties) of active agents on hallucinogenic activity. This approach is amechanistic and is simply

an attempt to correlate hallucinogenic activity/potency with chemical structure. The mechanistic model is similar to the conservative molecule approach except that it allows development of quantitative relationships between properties of drugs and pharmacological activities with potential mechanistic relevance (e.g., the influence of lipophilicity on receptor affinity for a series of active agents).

Although all three of these models may be of some predictive or mechanistic value, each requires animal or human data for initial input and, as such, cannot be considered a substitute for animal models. One of the more exciting techniques explored recently is the modeling of drug-receptor interactions using graphics models of neurotransmitter receptors. Because the precise three-dimensional structures of neurotransmitter receptors are unknown at this time, different models, and indeed different hypothetical modes of drug-receptor interaction, are possible (reviewed: Westkaemper and Glennon 1991). Thus, these models will require buttressing and validation by empirical methods such as site-directed mutagenesis, ligand binding utilizing chimeric receptors, or both. Nevertheless, such investigations have propelled the study of hallucinogens to the submolecular level.

ENIGMATIC AGENTS

Certain agents are continually identified by various animal models as being "active," when in fact there are little or no supporting human data. These agents fall into three broad categories. First, there are agents known to lack hallucinogenic activity in humans when administered in a single dose. Amphetamine, an example of such an agent, is active in several animal models (e.g., rabbit hyperthermia). Second, there are agents that generally are regarded as lacking hallucinogenic properties and that may even be widely used therapeutically, but for which there are scattered accounts of hallucinogenic episodes in humans. Lisuride is typical of this type of enigmatic agent. Third, there are those agents for which human data are very limited. Quipazine, for example, is active in many, if not most, animal models. It is this last category of agents that is most troublesome. Until additional clinical studies are conducted, it can never be known with certainty if these types of agents truly are without hallucinogenic effects. Nevertheless, these agents should continue to be used in future studies with animals in order to challenge new models as well as to gain additional insight about the agents themselves.

THE DRUG DISCRIMINATION PARADIGM

The DD paradigm was listed above along with other animal models of hallucinogenic activity. In fact, it has never been claimed that the paradigm is a model of hallucinogenic activity; however, it has been quite successful in qualitatively and quantitatively identifying hallucinogenic agents. The author has used this method extensively. Because some of the results described below require an understanding of this method, a brief description will be provided here (see Glennon et al. 1991*a* for a review and additional detail).

In the DD paradigm, animals are trained to elicit a particular response when administered a specific dose of a hallucinogenic agent and to elicit a different response when administered vehicle. Thus, animals can be trained to discriminate a drug from nondrug condition by, for example, responding on one of two levers in a two-lever operant procedure. Once animals have been trained to discriminate a specific hallucinogen from saline, various pharmacological investigations can be conducted (e.g., determination of median effective dose [ED,] values, time of onset, and duration of action).

Of particular interest are tests of stimulus generalization and tests of stimulus antagonism. In the former, also referred to as challenge tests or substitution tests, doses of different agents are administered to animals trained to discriminate a specific hallucinogen from saline. Such studies allow the identification of other agents that produce stimulus effects similar to those of a common training drug. That is, the animals are in effect identifying novel agents that presumably are perceived to possess similar properties. The results of these studies also allow for interagent potency comparisons for those agents identified as being active.

Tests of stimulus antagonism are quite similar and are based on the presumption that administration of the appropriate neurotransmitter antagonist in combination with the training drug will result in nondrug (i.e., vehicle-appropriate) responding. Such studies are useful for the identification of potential antagonists or, given the appropriate neurotransmitter antagonist, may be useful in identifying mechanisms of action. The DD paradigm has proven to be quite effective for the investigation of hallucinogenic agents as well as other drugs of abuse, including amphetamine, cocaine, phencyclidine (PCP), opioids, barbiturates, and ethanol (Glennon et al. 1991*a).*

Examples of each major category of classical hallucinogens (with the exception of the ß-carbolines) have been used as a training drug in DD studies. Mescaline, (+)LSD, 5-methoxy-DMT (5-OMe-DMT), and DOM, representative of the four major subclasses of classical hallucinogens, have seen the most extensive application. Stimulus generalization occurs among all four of these agents regardless of which is used as the training drug. This is one reason why such agents have been classified under the common heading of classical hallucinogens and has some bearing on the above mentioned suggestion that classical hallucinogens (although perhaps capable of producing slightly different effects) seem able to produce a common effect. This hypothesis has been further tested using rats trained to discriminate DOM from vehicle. A large number of agents, including simple tryptamine hallucinogens (for example, see figure 1 for 5-OMe-DMT, 4-methoxy-DMT (4-OMe-DMT) and DMT), a-methyltryptamines (figure 2), ergolines (see figure 1 for (+)LSD), phenylethylamines, phenylisopropylamines (see figure 3 for some examples), and ß-carbolines (see figure 4 for harmaline and 6-methoxyharmalan) have now been examined. To date, there have been no reports of false negatives. Furthermore, structure-activity relationships (SAR) have been formulated, mechanistic studies have been conducted, and, for a series of agents for which human data are available, there is a significant correlation ($r > 0.9$) between discrimination-derived ED, values and human hallucinogenic potencies (reviewed: Glennon 1991).

MECHANISM OF ACTION OF CLASSICAL HALLUCINOGENS

The 5-HT$_2$ Hypothesis

Classical hallucinogens are structurally similar to several major neurotransmitter substances, including serotonin (5-HT), norepinephrine (NE), epinephrine, and dopamine (DA). Over the years, it has been variously proposed that each of these substances (and other neurotransmitters or putative neurotransmitters such as histamine and tryptamine) may be involved in the mechanism of action of hallucinogenic agents. Indeed, there is some evidence that certain hallucinogens, most notably (+)LSD, interact at each of these types of receptors. Historically, however, there is little support for involvement of most of these neurotransmitters in the common actions of the classical hallucinogens. In contrast, 5-HT has been implicated consistently in the actions of hallucinogens ever since its discovery.

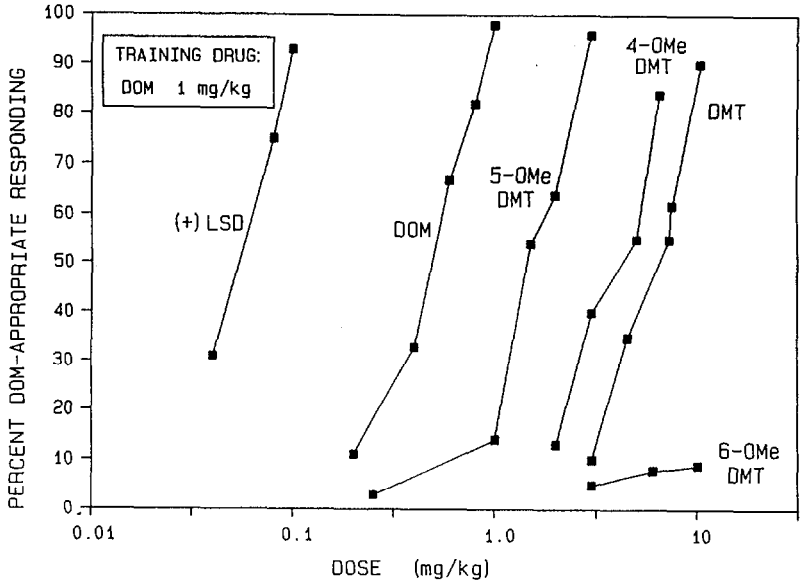

FIGURE 1. *DOM-stimulus generalization to examples of indolylalkylamines including (+)-LSD; N,N-dimethyltryptamine (DMT); 5-OMe-DMT; and 4-OMe-DMT as well as lack of DOM- stimulus generalization to 6-OMe-DMT. The dose-response curve for the training drug (i.e., DOM) is shown for the purpose of comparison.*

Controversy arose during the 1950s with the discovery of two distinct populations of peripheral 5-HT receptors (D receptors and M receptors). Do hallucinogens act at 5-HT receptors? If so, do they act as 5-HT agonists or antagonists? During the 1980s, identification of multiple populations of central 5-HT receptors (5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_2, 5-HT_3, and 5-HT_4) only served to complicate the issue further. Most of the 5-HT_1 (and probably 5-HT_4) receptors belong to a G-protein coupled superfamily of receptors involving an adenylate cyclase second messenger system; 5-HT_2 and 5-HT_{1C} receptors (now referred to as 5-HT_{2A} and 5-HT_{2C} receptors, respectively) also belong to this family but are linked to a phosphoinositol (PI) second messenger system. 5-HT_3 receptors are distinct in being ligand-gated ion channel receptors.

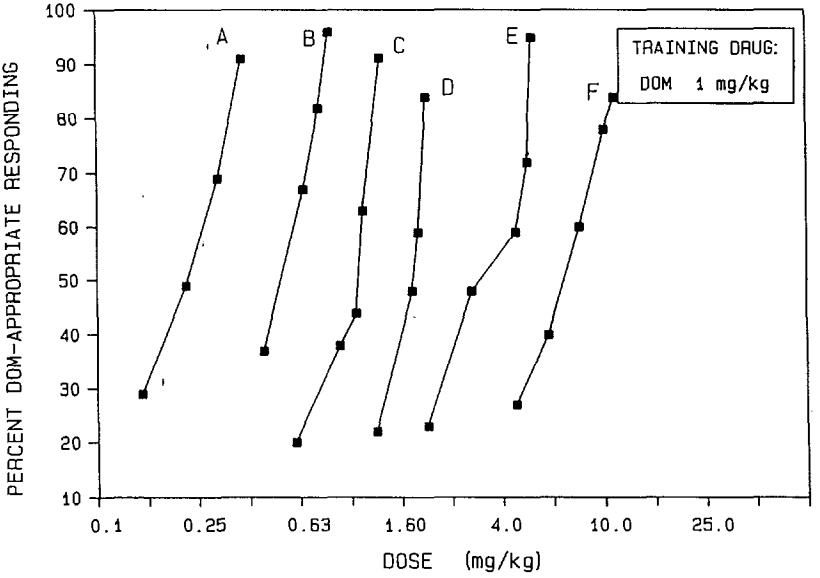

FIGURE 2. *DOM-stimulus generalization to (+)5-methoxy-α-methyltryptamine (5-OMe-α-MT; A), (±)5-OMe-α-MT (B), (-)5-OMe-α-MT (C), (+)α-MT (D), (±)α-MT (E), and racemic α-ethyltryptamine (F).*

The issue now becomes even more complicated: which population(s) of 5-HT receptors are involved in the actions of classical hallucinogens? On the basis that the discriminative stimulus effects of DOM and DOM-stimulus generalization to (+)LSD, 5-methoxy DMT, and mescaline could be potently antagonized by 5-HT_2 antagonists, it was proposed that the classical hallucinogens act as agonists at 5-HT_2 receptors (Glennon et al. 1983). To support this hypothesis, the binding of various hallucinogens at the different populations of 5-HT receptors was examined using radioligand binding techniques. Indolylakylamine hallucinogens are fairly nonselective and bind with high affinity at multiple populations of 5-HT receptors. In contrast, the phenylisopropylamine hallucinogens such as DOM, DOB, and DOI bind rather selectively at 5-HT_2 receptors. Furthermore, there is a significant correlation ($r > 0.9$) between 5-HT_2 receptor affinity and both discrimination-derived ED, values and human hallucinogenic potencies (Glennon 1990). For the first time, there was now evidence for the 5-HT_2 hypothesis of hallucinogenic activity.

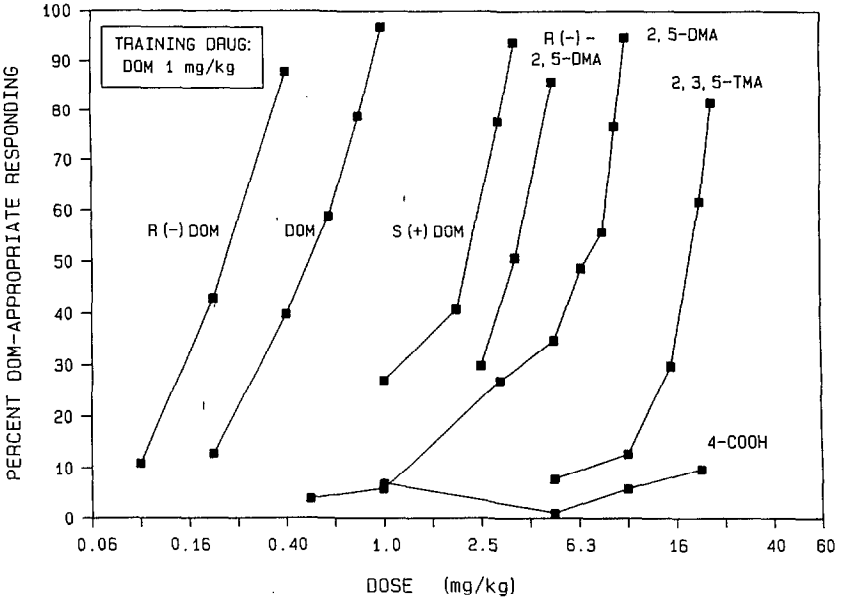

FIGURE 3. *DOM-stimulus generalization to R(-)DOM; (±)DOM; S(+)DOM; R(-)2,5-DMA; (±)2,5-DMA; and 2,3,5-TMA; and lack of stimulus generalization to 2,5-DMA 4-carboxylic acid ("4-COOH"), a metabolite of DOM*

DOB and its demethylated counterpart, α-desmethyl-DOB, produce similar yet distinguishable effects in humans. Consistent with the common component hypothesis, these agents produce similar stimulus effects in animals and bind with similar potencies at 5-HT_2 receptors; however, α-desmethyl-DOB binds in a less selective manner than DOB (Glennon et al. 1988). Thus, it could be the less selective nature of α-desmethyl-DOB that accounts for its distinguishability from DOB.

5-HT_2-Related Problems

Several problems have arisen regarding the 5-HT_2 hypothesis:

Do hallucinogens act as 5-HT_2 agonists or antagonists?
Are there subpopulations of 5-HT_2 receptors?
May some other population of 5-HT receptors (instead of 5-HT_2 be involved in the actions of hallucinogens?

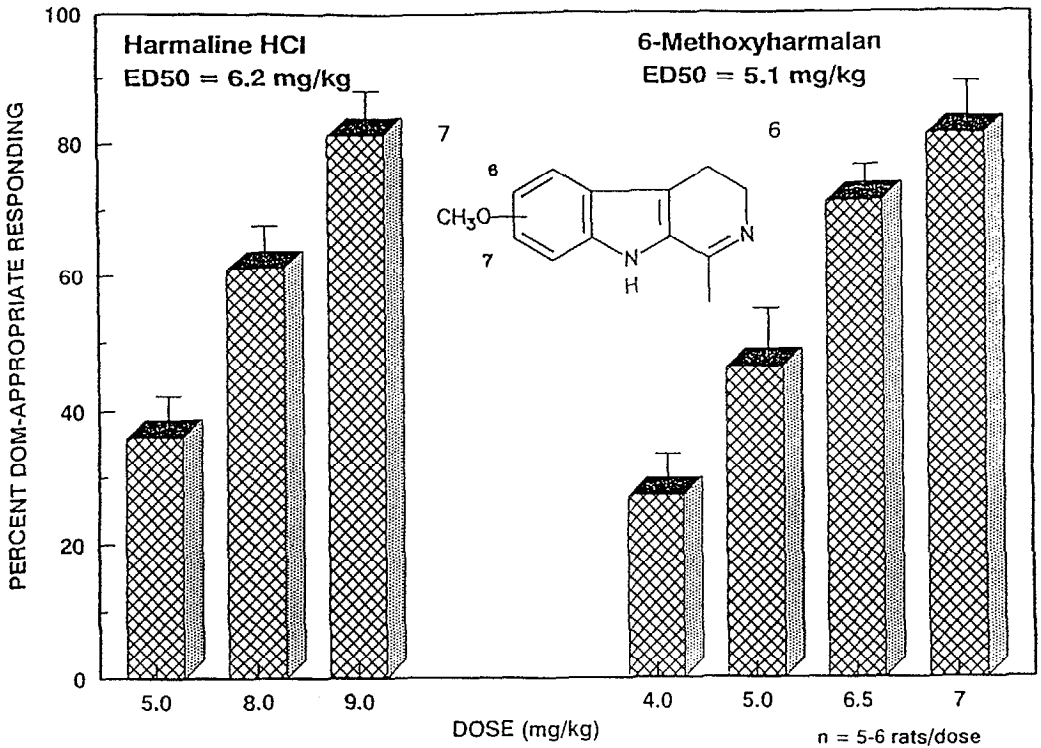

FIGURE 4. *DOM-stimulus generalization to two hallucinogenic ß-carbolines, harmaline and 6-methoxyharmalan, in studies using rats trained to discriminate 1 mg/kg of DOM from saline.*

On the basis of previous DD studies, it was originally suggested that classical hallucinogens act as 5-HT_2 agonists. However, Pierce and Peroutka (1988) recently challenged this concept and have suggested that hallucinogens, particularly (+)LSD, act as 5-HT_2 antagonists. This agonist-versus-antagonist controversy was reexamined, and it was concluded that hallucinogens are not 5-HT_2 antagonists; classical hallucinogens are agonists, or at least partial agonists, at 5-HT_2 receptors (Glennon 1990). Certain hallucinogens, including LSD, may possess a low intrinsic activity; thus, given in combination with a full agonist, such agents might occasionally appear to behave as antagonists in some pharmacological assays.

Lyon and colleagues (1987) have proposed that 5-HT_2 receptors exist in a low-affinity state and an agonist high-affinity state (i.e., the two-state hypothesis). [^{3}H]Ketanserin, a 5-HT_2 antagonist, labels both states of the receptors, whereas the agonist radioligands [^{3}H]DOB and [^{125}I]DOI apparently label the agonist high-affinity state. Pierce and Peroutka (1989) later conducted related investigations using [^{77}Br]DOB and proposed an alternative explanation: there exist two different populations (i.e., subpopulations) of 5-HT_2 receptors (the two-site hypothesis). The results of recent cloning studies favor the two-state concept in that a single 5-HT_2 receptor is expressed that behaves in a manner reminiscent of a two-state receptor population (reviewed: Weinshank et al. 1992). It might be noted, however, that the possibility of two different (overlapping) binding domains has not yet been excluded; that is, agonists and antagonists may bind in a slightly different manner at the same population (or state) of 5-HT_2 receptors.

Finally, there is the issue of involvement of other (or additional) populations of 5-HT receptors in the actions of hallucinogens. This is discussed below.

Involvement of 5-HT_{1C} Receptors

Shortly after the 5-HT_2 hypothesis was proposed (Glennon et al. 1983, 1984), Pazos and coworkers (1984) described their discovery of 5-HT_{1C} receptors. The binding of hallucinogens at these receptors was subsequently examined, and little difference between their 5-HT_2 and 5-HT_{1C} affinities was found (Titeler et al. 1988); indeed, later studies have shown less than a tenfold difference in receptor affinity for a large series of phenylalkylamine derivatives (Glennon et al. 1992). As with 5-HT_2 receptor affinities, 5-HT_{1C} affinities also are correlated both with

discrimination-derived ED, values and human hallucinogenic potencies. In addition, Burris and Sanders-Bush (1988) reported that DOM acts as a 5-HT_{1C} agonist. Furthermore the 5-HT_2 hypothesis was based, in part, on the finding that 5-HT_2 antagonists (such as ketanserin and pirenperone) antagonize the stimulus effects of hallucinogens. It is now recognized that these 5-HT_2 antagonists are described more accurately as 5-HT_2 and 5-HT_{1C} antagonists. Thus, the likelihood exists that 5-HT_2 and/or 5-HT_{1C} receptors are involved in the actions of hallucinogenic agents. It may be this interaction that constitutes the common "key" mentioned at the beginning of this chapter, and it may be this common interaction that allows animals to reliably discriminate classical hallucinogens from the vehicle.

It is quite difficult to ascribe a specific role for 5-HT_{1C} versus 5-HT_2 receptors in the mechanism of action of hallucinogens due to the lack of agents that display selectivity for one of these populations of receptors over the other. Nearly all agents that bind at 5-HT_2 receptors bind at 5-HT_{1C} receptors. However, there are a few agents that might offer some hope in resolving this problem. The DA 5-HT_{1A} antagonist spiperone binds with approximately 500-fold selectivity for 5-HT_2 versus 5-HT_{1C} receptors. An attempt was made to antagonize the stimulus effects of DOM using various doses of spiperone with the intention that it might be more difficult to antagonize the DOM stimulus if the stimulus was 5-HT_{1C} mediated. Unfortunately, the results of these studies were inconclusive due to the severe disruptive effects of low doses of spiperone in combination with DOM (Glennon 1991).

Another agent of interest is l-(3-trifluoromethylphenyl)piperazine (TFMPP). Although TFMPP binds at multiple populations of 5-HT receptors, evidence suggests that TFMPP is a 5-HT_{1C} agonist but a 5-HT_2 antagonist (or, at best, a 5-HT_2 partial agonist). Administration of TFMPP to animals trained to discriminate DOM from saline failed to result in stimulus generalization. In a parallel study, administration of DOM (or DOI) to animals trained to discriminate TFMPP from vehicle resulted in only partial generalization followed at slightly higher DOM (or DOI) doses by disruption of behavior. Thus, the results were again inconclusive. In a third series of studies, rats trained to discriminate 0.5 milligrams per kilogram (mg/kg) of TFMPP from the vehicle were administered doses of DOM in combination with 0.2 mg/kg of TFMPP (ED, dose = 0.17 mg/kg). The rationale for this investigation was that lower (i.e., nondisruptive) doses of DOM should potentiate the effect of the near-ED, dose of TFMPP if both agents act via a common

mechanism. The results (shown in figure 5) were somewhat surprising in that low doses of DOM, rather than potentiating the effect, actually antagonized the effect of TFMPP. For all practical purposes, the results of this study also were inconclusive; however, they suggest that DOM and TFMPP are likely producing their stimulus effects via different mechanisms.

There is one additional piece of information that perhaps has some bearing on the 5-HT_2 versus 5-HT_{1C} controversy. Several years ago, Glennon and Hauck (1985) reported that the DOM stimulus generalizes to lisuride. This was a rather unexpected finding. Subsequently, the author and coworkers reevaluated lisuride as a potential DOM antagonist and found that it attenuates the DOM stimulus by 50 percent at very low doses (i.e., at one-sixtieth of the dose that results in stimulus generalization). This led to speculation that lisuride may be acting as a partial agonist (Glennon 1991). Sanders-Bush has recently demonstrated (this volume) that, whereas lisuride is a pure 5-HT_{1C} antagonist, it behaves as a partial agonist at 5-HT_2 receptors. These results are consistent with the present DD studies. Thus, although hallucinogens unquestionably bind at both populations of receptors and whereas a mechanistic role for 5-HT_{1C} receptors cannot yet be eliminated, it would appear on the basis of all the above mentioned studies that the DOM stimulus involves primarily a 5-HT_2 mechanism.

Before leaving the topic of 5-HT_2 and 5-HT_{1C} receptors, it might be mentioned that certain of the animal models described earlier appear to involve actions mediated by these receptors. For example, the head-twitch response has been proposed to involve such a mechanism (Glennon 1992). In retrospect, some of these models may be less farfetched and more mechanistically relevant than once suspected.

Involvement of Other 5-HT Receptors

It was recently reported that there may be functional interactions between different populations of 5-HT receptors such that action at one may modulate activation of another (reviewed: Glennon et al. 1991*b*). Thus, interaction of an agonist at one population of 5-HT receptors may modulate the effect of the interaction of a second agonist at a different population of receptors. This could have far-reaching consequences. For example, what is the effect of a nonselective agonist that interacts at more than one population of receptors at the same time? What about a nonselective agent that is an agonist at one population and an antagonist

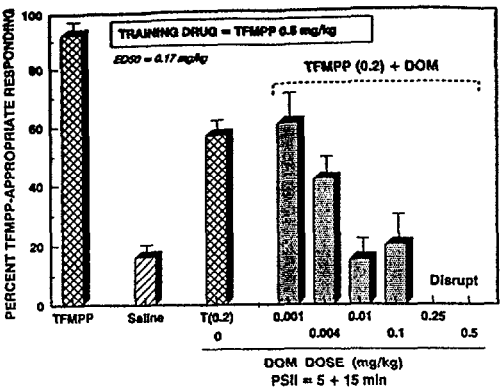

FIGURE 5. *The effect of DOM in combination with a near-ED_{50} dose of TFMPP in rats trained to discriminate TFMPP (0.5 mg/kg) from saline. TFMPP elicits > 90 percent TFMPP-appropriate responding (ED, = 0.17 mg/kg); 0.2 mg/kg of TFMPP [T(0.2)] elicits 57 percent TFMPP-appropriate responding. Administration of various doses of DOM 5 min prior to administration of 0.2 mg/kg of TFMPP results in attenuation of TFMPP-appropriate responding. Administration of 0.25 and 0.5 mg/kg of DOM in combination with 0.2 mg/kg of TFMPP resulted in disruption of behavior (i.e., no responding).*

at another? Experiments necessary to sort out these types of interactions could be rather labor intensive and their interpretation quite complicated. Worse yet are cases where such types of interactions are possible but unrecognized.

It was previously shown that the DOM stimulus does not generalize to the 5-HT_{1A} agonist 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT), and that an 8-OH-DPAT stimulus does not generalize to DOM. Furthermore, DOM does not bind at 5-HT_{1A} receptors, nor does 8-OH-DPAT bind with significant affinity at 5-HT_2 receptors. More recently, it was demonstrated that very low doses of 8-OH-DPAT amplify the stimulus effects of DOM in DOM-trained rats. For example, animals given 0.05 mg/kg of 8-OH-DPAT in combination with the ED, dose of DOM behave as if they have received the training dose of DOM (i.e., stimulus generalization occurs upon administration of the ED, dose of DOM) (see inset, figure 6). Furthermore, pretreatment of animals with 0.05 mg/kg of 8-OH-DPAT results in a leftward shift of the DOM dose-response curve (figure 6). These results would seem to suggest that low doses of the 5-HT_{1A}-selective agonist influence the stimulus effects of DOM. Additional studies are required to further understand the details of this interaction.

Similar studies were conducted with 5-HT_3 agents. For example, very low doses of the 5-HT_3 antagonist zacopride attenuate the stimulus effects of DOM even though zacopride does not bind at 5-HT_2 receptors, and DOM does not bind at 5-HT_3 receptors. A dose of 0.001 mg/kg of zacopride in combination with the training dose of DOM results in about 30 percent DOM-appropriate responding. Higher doses appear to have less of an attenuating effect (figure 7). The 5-HT_3 (partial) agonist meta-chlorophenylbiguanide (mCPBG) also has an unusual effect on the DOM stimulus (figure 8). A dose of 0.5 mg/kg of mCPBG seems to attenuate the stimulus effects of 1 mg/kg of DOM; higher doses have less of an effect. However, administered alone, mCPBG seems to result in partial generalization. Doses higher than those shown resulted in disruption of behavior.

Parallel studies were conducted using rats trained to discriminate the structurally related agent N-methyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane (MDMA) from saline. Zacopride and LY 278584, at doses of between 0.0003 and 0.001 mg/kg, decrease MDMA-appropriate responding to about 20 percent (figure 9). The effect of mCPBG (figure 10) is not unlike that seen with DOM. The results suggest a possible

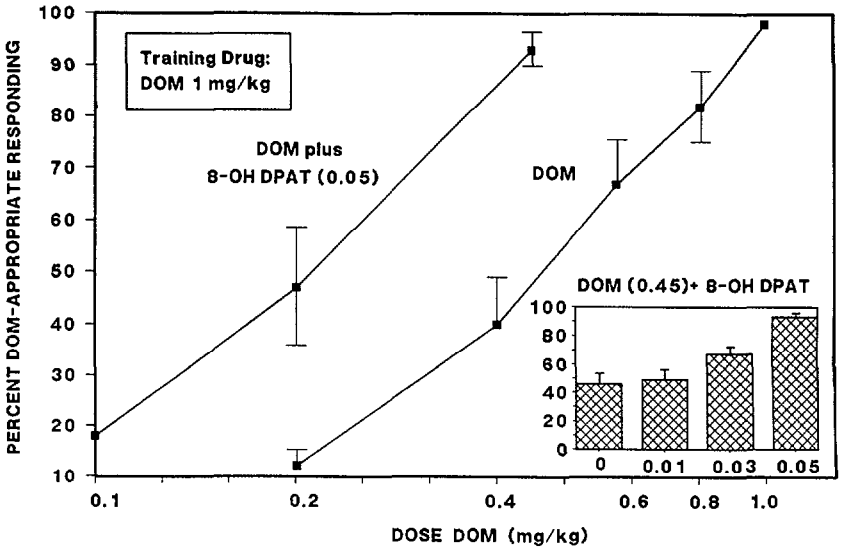

FIGURE 6. *Effect of the 5-HT$_{1A}$ agonist 8-OH-DPAT in combination with DOM in rats trained to discriminate DOM from saline. Dose-response curve for DOM (right) and for DOM in animals pretreated with 0.05 mg/kg of 8-OH-DPAT (left). Inset shows effect of different doses of 8-OH-DPAT administered in combination with the ED, dose (0.45 mg/kg) of DOM. Data previously reported (Glennon 1991).*

modulatory effect by 5-HT$_3$ receptors on the DOM and MDMA stimulus. It might be noted, for purpose of comparison, that zacopride had essentially no effect on amphetamine-appropriate responding in rats trained to discriminate (+)amphetamine from vehicle. These types of unexpected interactions open up entirely new lines of investigation regarding classical hallucinogens and may (?) hint at a possible role for 5-HT$_3$ antagonists in the treatment of drug abuse involving hallucinogens.

SAR AND STRUCTURALLY RELATED AGENTS

SAR have been formulated for hallucinogenic activity, DOM-stimulus generalization, and 5-HT$_2$/5-HT$_{1C}$ binding. The best investigated agents are the phenylalkylamines and, to a somewhat lesser extent, the simple tryptamines. ß-Carbolines and ergolines have received much less attention. Abuse of ß-carbolines does not seem to be a significant

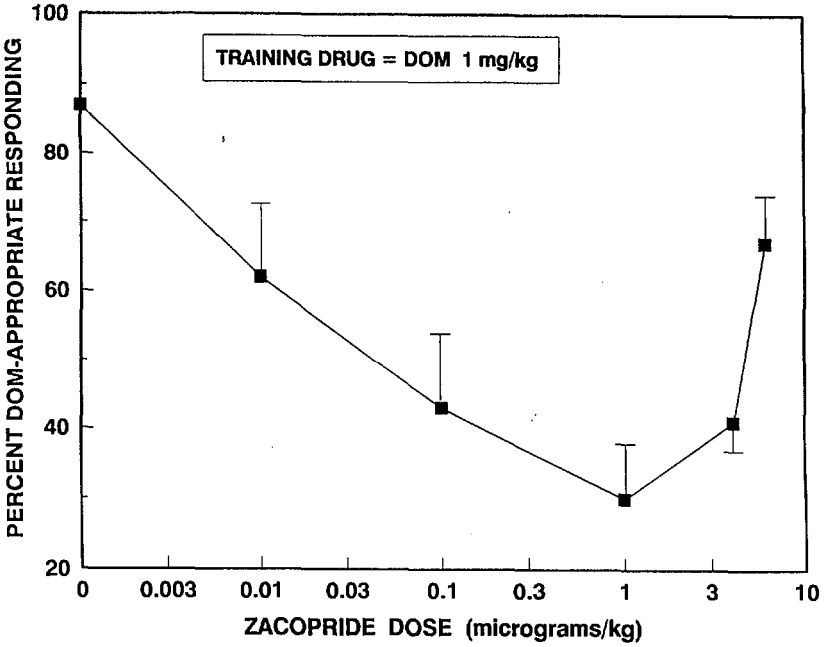

FIGURE 7. *Effect of the 5-HT_3 antagonist zacopride administered in combination with the training dose of DOM to rats trained to discriminate 1 mg/kg of DOM from saline.*

problem, and it is perhaps this reason that accounts for the lack of interest or urgency to study these agents. Ergolines, on the other hand, can offer, a significant synthetic challenge and relatively few agents are readily available. The SAR of classical hallucinogens has been reviewed (Nichols and Glennon 1984).

Many investigations of classical hallucinogens are limited to a small handful of standard agents (e.g., LSD, mescaline, DOM). Far fewer studies have examined some of the more novel or structurally distinct agents, or have examined series of agents. It would seem prudent to examine additional agents and structurally related analogs in order to define exactly what structural features contribute to activity. A classic example is the phenylisopropylamine amphetamine. The amphetamine structural backbone is contained in, for example, the hallucinogen DOM and the designer drug MDMA; and yet each of these three agents produces effects in animals and humans that are clearly distinguishable from one another (Shulgin and Shulgin 1991). As the structure of one of these agents is gradually modified to one of the others, at what point does

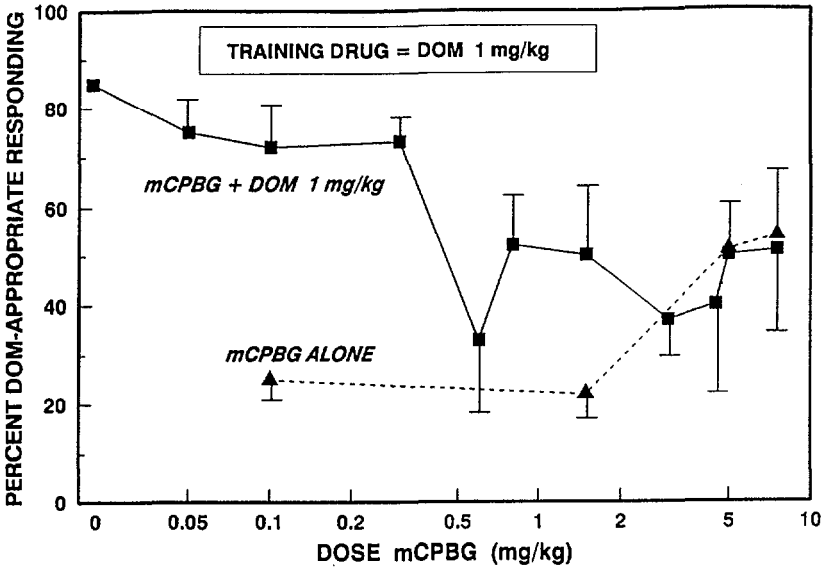

FIGURE 8. *Effect of the 5-HT_3 partial agonist meta-chlorophenylbiguanide (mCPBG), administered either alone (broken line) or in combination with the training dose of DOM (solid line) in rats trained to discriminate DOM (1 mg/kg) from vehicle.*

an amphetamine-like agent become, for example, a hallucinogenic agent? Is there some structure that possesses both properties?

This would seem to be the case. It has been demonstrated in tests of stimulus generalization that 1-(3,4-methylenedioxyphenyl)-2-aminopropane (MDA) produces both amphetamine-like and DOM-like effects as well as MDMA-like stimulus effects. The amphetamine-like effect rests primarily with the S(+)isomer, whereas the R(-)isomer is the more DOM-like. Furthermore, it was recently demonstrated that rats can be trained to discriminate 1.25 mg/kg of S(+)MDA from 1.25 mg/kg of R(-)MDA using a three-lever operant paradigm (Glennon and Young, unpublished findings). The stimulus effects of the isomers of MDA are thus clearly distinguishable from one another.

Agents were also examined using rats trained to discriminate either DOM, (+)amphetamine, or MDA from vehicle. Some of these results are shown in figure 11. It can be seen that agents such as (+)LSD produce DOM-like effects, and cocaine produces (+)amphetamine-like effects, but

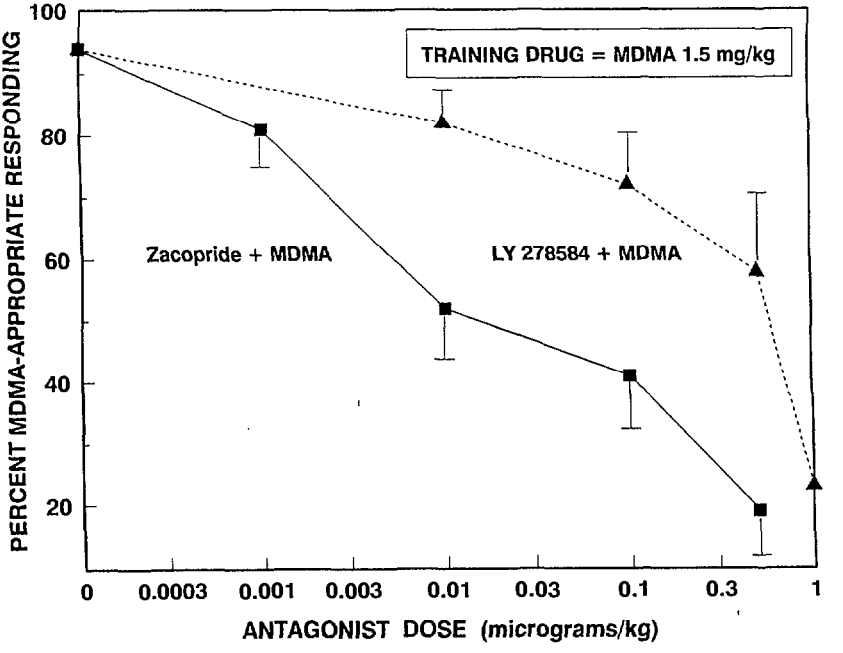

FIGURE 9. *Effect of the 5-HT_3 antagonists zacopride and LY 278584 administered in combination with the training dose of MDMA in rats trained to discriminate MDMA (1.5 mg/kg) from saline.*

both agents result in stimulus generalization in rats trained to discriminate racemic MDA from vehicle. Furthermore, agents such as 1-(3,4-dimethoxyphenyl)-2-aminopropane (3,4-DMA), which produces neither amphetamine-like nor DOM-like stimulus effects, produces MDA-like stimulus effects (figure 11). Clearly, minor structural changes have a profound influence on the stimulus effects of these agents.

Agents such as α-ethyltryptamine (ET), which is currently popular on the clandestine market, produce DOM-like effects (figure 2) but also result at least in partial generalization in rats trained to discriminate either (+)amphetamine or MDMA from vehicle (figures 12 and 13). Perhaps certain tryptamine derivatives will eventually be discovered to bridge several pharmacological categories in a manner similar to that of MDA, and the results of studies with ET (figures 12 and 13) certainly suggest that its individual optical isomers be examined.

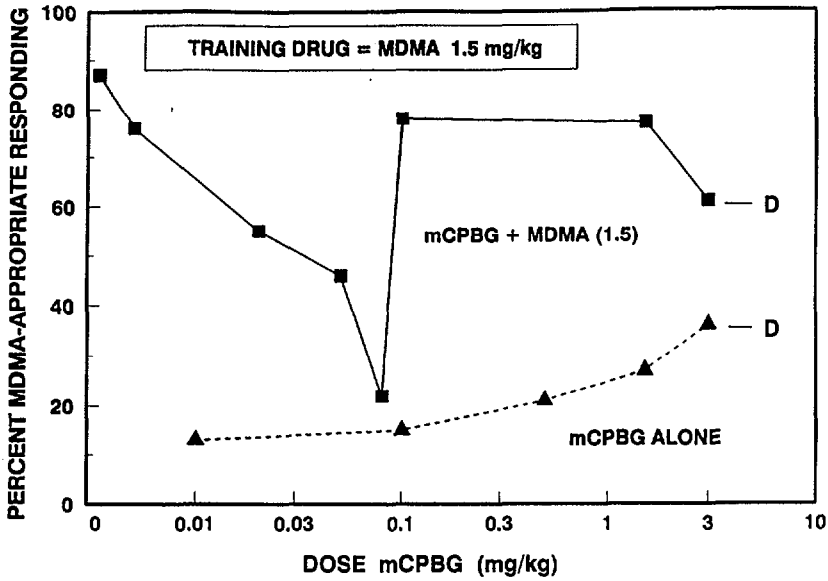

FIGURE 10. *Effect of the 5-HT_3 partial agonist mCPBG administered either alone (broken line) or in combination with the training dose of MDMA (solid line) in rats trained to discriminate MDMA (1.5 mg/kg) from saline.*

Thus, there is a need to continue examination of new structural analogs not only with the intent of formulating and challenging SARs, but also for the purpose of elucidating mechanisms of action and classifying what agents produce what effects.

FUTURE DIRECTIONS

The present technical review focused entirely on classical hallucinogens. Figure 14 shows the extensive nature of the investigations addressed at this meeting. With the above discussion as background, there are several problems that need to be addressed:

- An exacting definition is still required for the effects produced by hallucinogenic agents. Furthermore, addtional work needs to be done on what agents fall into this category on the basis of whether or not they produce a common effect.

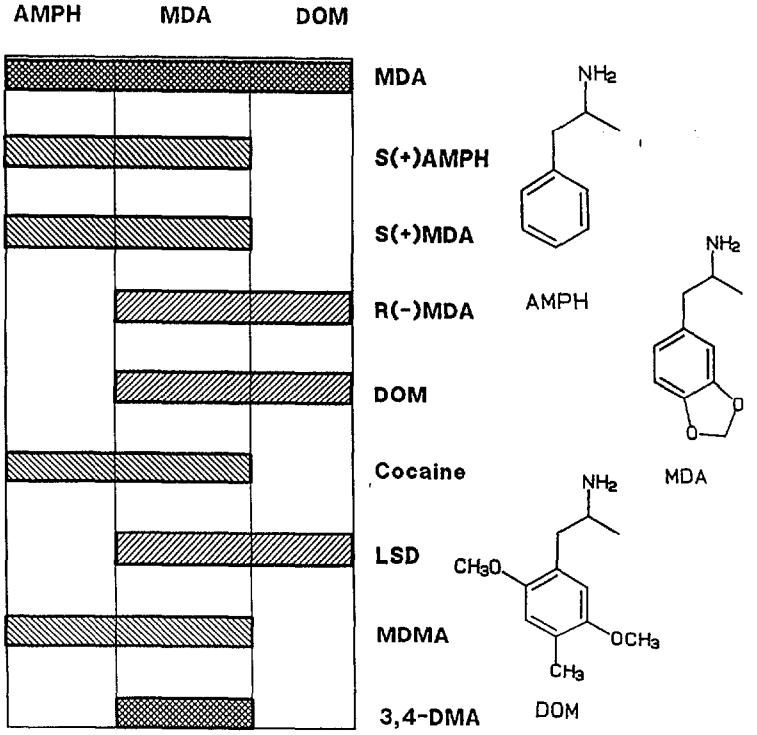

FIGURE 11. *Stimulus-generalization profiles of various agents in rats trained to discriminate either (+)amphetamine sulfate (AMPH), MDA HCl, or DOM HCl from saline. Once animals were trained to discriminate one of the training drugs (AMPH, MDA, or DOM), tests of stimulus generalization were conducted with the agents listed on the right. A darkened bar represents the group(s) of animals in which stimulus generalization (i.e., > 80 percent drug-appropriate responding) occurred. For example, both the AMPH stimulus and the MDA stimulus, but not the DOM stimulus, generalized to cocaine.*

- Additional clinical data are required to validate previously published animal data. Animal models are now realized to possess shortcomings, but there is a significant amount of animal data available that could assist the understanding of hallucinogens.

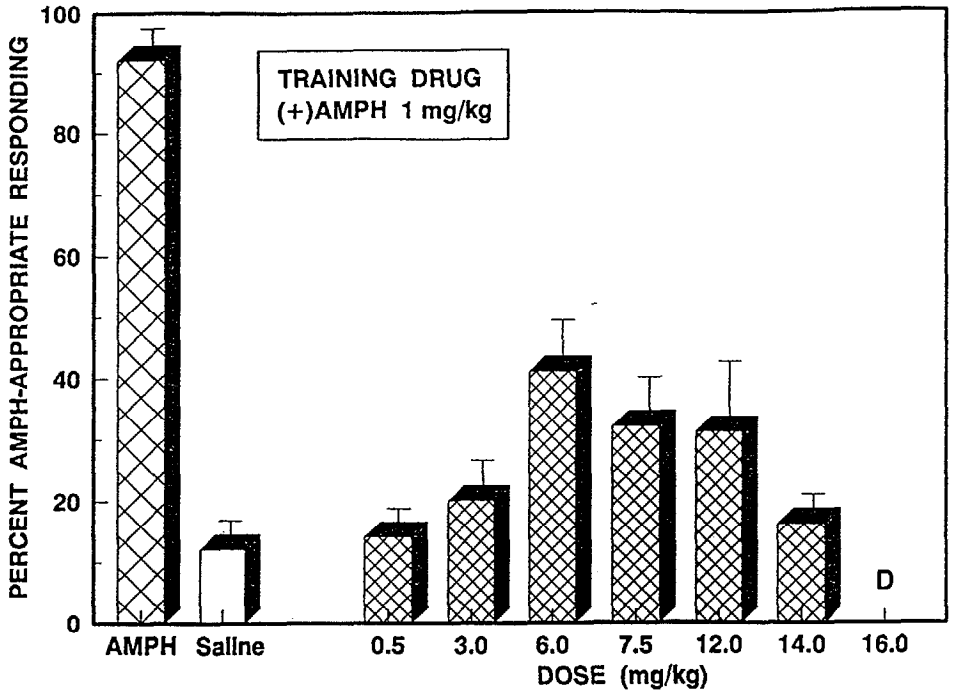

FIGURE 12. *Stimulus-generalization studies with racemic α-ethyltryptamine acetate in male Sprague-Dawley rats (n = four to five animals per dose) trained to discriminate (+)amphetamine sulfate from saline. At doses ≥ 7.5 mg/kg, the animals' response rates were depressed by about 50 percent; disruption of behavior occurred at 16 mg/kg.*

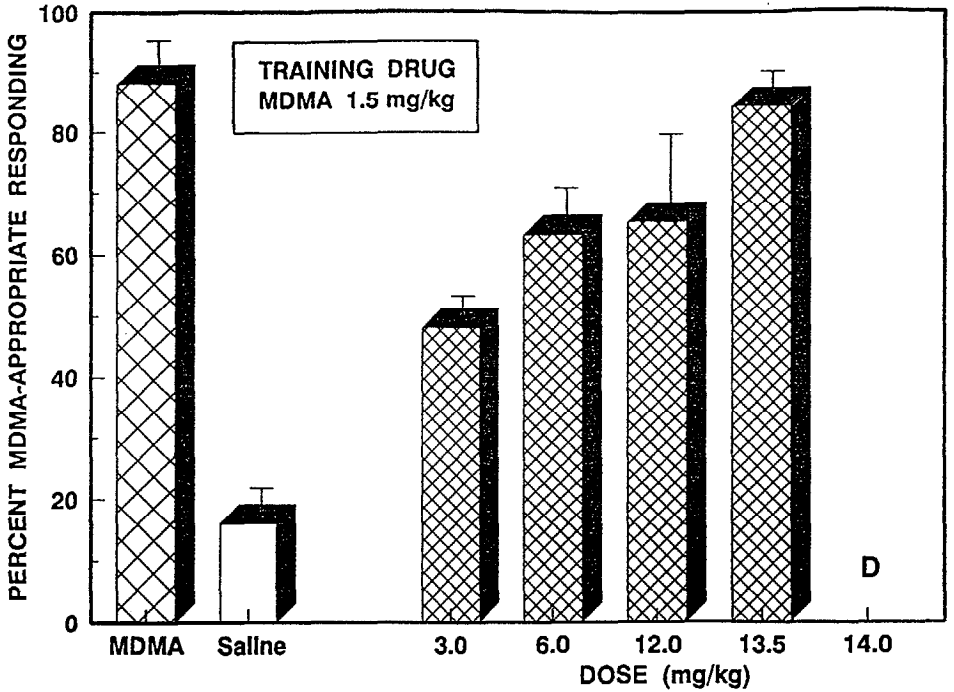

FIGURE 13. *Stimulus-generalization studies with racemic α--ethyltryptamine acetate in male Sprague-Dawley rats (n = three to four animals per dose) trained to discriminate MDMA hydrochloride from saline. At 13.5 mg/kg, only two of four animals responded; response rates were comparable to control response rates except where disruption of behavior occurred (i.e., at 14 mg/kg; n = 1/3).*

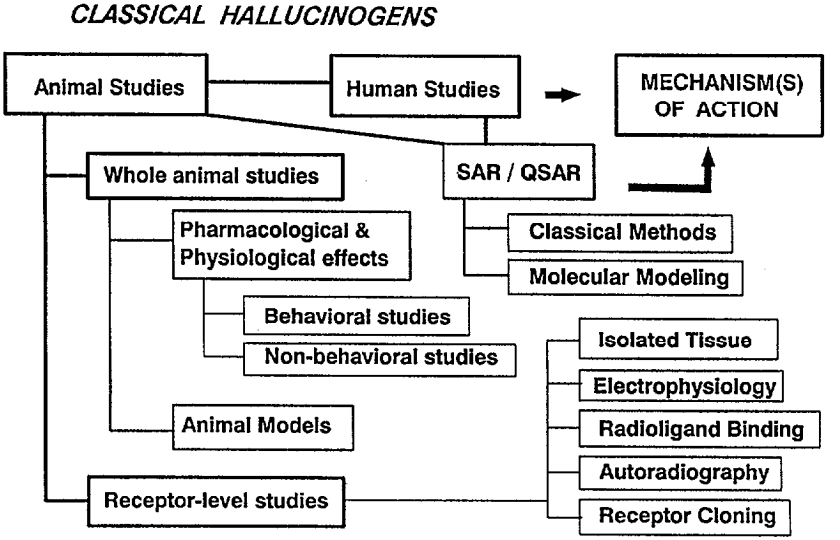

FIGURE 14. *An outline of various studies conducted with classical hallucinogens (described at the NIDA Technical Review on Advances in Data Analysis for Prevention Intervention Research).*

- Some SARs have been formulated, but more work needs to be done. Minor structural variation has a profound and intriguing effect on pharmacological activity. Minimal data are available on quantitative structure-activity relationships (QSAR).

- The mechanism of action of classical hallucinogens is not fully understood. Although 5-HT_2 and 5-HT_{1C} receptors have been implicated as playing a major role and are currently the primary mechanistic focus of many investigations, the role of other neurotransmitters requires examination.

- Functional interactions between receptor populations, with consequent modulation of agonist effects, may represent an entirely new method for treating drug abuse. Such functional interactions deserve further investigation.

- The locus of hallucinogen action in brain requires additional study. New scanning and autoradiographic techniques may aid in this regard. Second messenger systems, as well as differential regulation of receptor number versus second messenger systems, should be pursued.

- Is there a prototypic classical hallucinogen? Many investigations with hallucinogens involve the same small number of agents, in particular LSD. Should LSD be considered a prototype agent? Or is it possible that investigation of one or two agents in great depth may lead researchers astray by providing information that is unique to a specific agent, rather than information that may be more germane to classical hallucinogens as a group? The same may be said for animal models. Perhaps future studies should not rely solely on investigating the same small number of standard agents nor rely only on a few pharmacological test procedures.

NOTE

Since the original submission of this manuscript, the terms "5-HT_2 and 5-HT_{1C} receptors" have been replaced by "5-HT_{2A} and 5-HT_{2C} receptors," respectively.

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