CHAPTER 10

Classical Hallucinogens*

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A. Introduction

Hallucinogenic agents, although typically nonaddicting, constitute a notable class of abused substances. Not only do hallucinogens possess a rich and fascinating folkloric history, but they constitute one of the oldest known classes of pharmacologically active agents. The earliest written account of psychoactive agents dates back 3500 years, and there is evidence that hallucinogenic plants were in use as long ago as 8000 B.C. The first mention of the use of hallucinogenic crude plant products in the New World was made, appropriately enough, by a member of the Columbus expedition. For a treatment of the historical and anthropological aspects of hallucinogens, see EFRON et al. (1967), FURST (1976) and HARNER (1973).

Although a small handful of substances has gained widespread name recognition – for example, the term "hallucinogen" often conjures up notions of drugs such as LSD and mescaline – there are perhaps hundreds of agents and naturally occurring substances that may be called hallucinogenic. Lately, some new designer drugs (i.e., controlled substance analogs) have been shown to possess hallucinogen-related structures. Thus, investigations with hallucinogens not only aid our understanding of hallucinogenic agents per se but can also have a bearing on these novel designer drugs. Apart from drug abuse considerations, hallucinogens may also be useful in the development of neuropsychiatric agents. Because certain hallucinogens act as 5-HT_2 serotonin (5-HT) agonists, and because 5-HT_2 antagonists may be effective in the treatment of schizophrenia, depression, and anxiety, antagonism of hallucinogen-induced effects in animals is becoming increasingly useful for the identification of novel serotonin antagonists.

Structurally, classical hallucinogens (see Sect. B for definitions) are commonly divided into two categories: those possessing an indolylalkylamine nucleus and those possessing a phenylalkylamine moiety (Fig. 1). The indolylalkylamines may be further divided into the: (1) simple N-substituted tryptamines, e.g., *N*,*N*-dimethyltryptamine (DMT), 5-methoxy DMT

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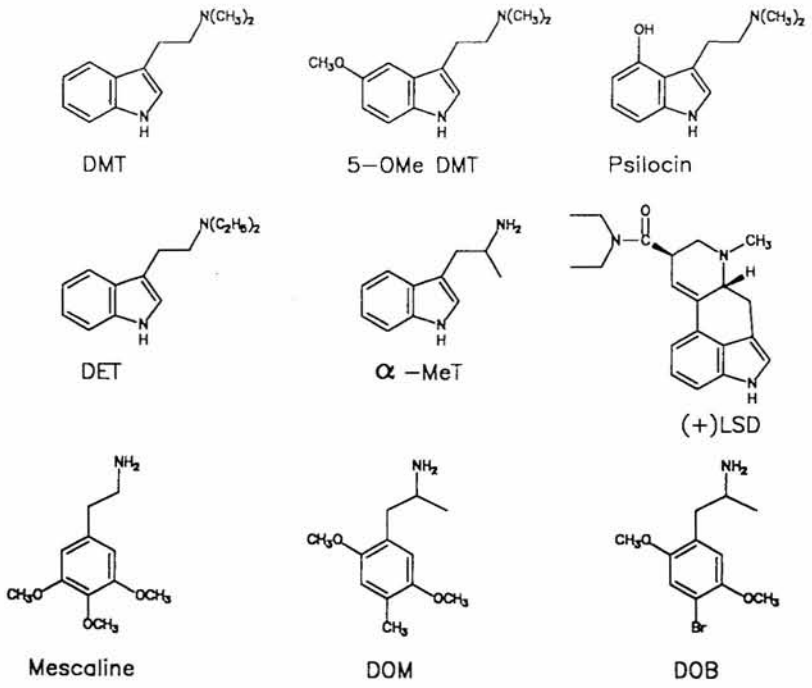


Fig. 1. Examples of indolylalkylamine classical hallucinogens: *N,N*-dimethyltryptamine (*DMT*, 5-methoxy DMT, psilocin, *N,N*-diethyltryptamine (*DET*), α-methyltrypta-mine (*α-MeT*), and (+)lysergic acid diethylamide (*LSD*); and of phenylalkylamine classical hallucinogens: mescaline, 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (*DOM*), and 1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane (*DOB*)

(5-OMe DMT) psilocin (4-OH DMT), or *N,N*-diethyltryptamine, (DET), (2) α-methyltryptamines (α-MeT) e.g., 5-methoxy α-MeT, (3) ergolines e.g., (+)lysergic acid diethylamide (LSD), and (4) β-carbolines, e.g., harmaline-related alkaloids. The phenylalkylamines may be subdivided according to whether or not they possess an α-methyl group on the alkyl chain that separates the aromatic ring from the terminal amine; phenylalkylamines without the α-methyl group are termed phenylethylamines, e.g., mescaline, whereas those with the α-methyl group are termed phenylisopropylamines or phenylaminopropanes, e.g., 1-(2,5-dimethoxy-4X-phenyl)-2-aminopropanes, where X can be methyl, bromo or iodo, i.e., DOM, DOB, and DOI, respectively. For a general review of hallucinogens, see BRIMBLECOMBE and PINDER (1975); for a discussion of classical hallucinogens, see NICHOLS and GLENNON (1984) and SHULGIN and SHULGIN (1991). The present chapter deals exclusively with classical hallucinogens and structurally related agents.

B. Definitions

The term "classical hallucinogen" is being employed with increasing frequency. The purpose of this is to distinguish between different classes of agents that produce hallucinogenic effects. This is an important consideration for certain investigations, such as those aimed at elucidating mechanisms of action. For example, chronic administration (but, normally, not administration of single doses) of amphetamine can produce hallucinations (i.e., "amphetamine psychosis"); hallucinatory episodes may accompany the toxic delirium associated with the use of certain nonhallucinogenic agents; and the intoxication produced by phencyclidine (PCP) or certain opiates seems to be different from that produced by, for example, LSD. Each of these hallucinogenic effects is probably mechanistically distinct. Unfortunately, to date, there is no definition that adequately and accurately describes the actions of these agents. HOLLISTER (1968) proposed a set of criteria that should be met in order for an agent to be considered hallucinogenic: (1) in proportion to other effects, changes in thought, perception and mood should predominate, (2) intellectual or memory inpairment 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. Classical hallucinogens typically possess an indolealkylamine or phenylalkylamine moiety; as will be described below, they also bind at 5-HT_2 receptors and produce stimulus effects similar to those of DOM. However, specific inclusion criteria have yet to be defined.

Even within the category of agents called classical hallucinogens, it is recognized that not all agents necessarily produce identical effects. Indeed, not all classical hallucinogens produce hallucinations. Although hallucinogens may produce visual, and to a lesser extent, auditory hallucinations, they also produce closed-eye imagery, synesthesia, and other perceptual alterations. 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). Thus, clearly, there exist some differences in effect. How can these differences be rationalized? There are several likely explanations: (1) effects may be dose- or route-dependent, (2) somatic or other 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 nonidentical mechanisms that share a common mechanistic component. Because there is some evidence for similarity of effect, the last explanation, i.e., the *common component hypothesis*, provides a framework for mechanistic investigations (GLENNON 1984). Identification of a common mechanistic component may be important to our understanding of these agents. Agents that produce dissimilar effects are likely acting via a different mechanism; such agents may need to be

categorized separately, and such categorization may influence future treatment modalities. This is particularly true of designer drugs that contain structural elements similar to hallucinogens and, at the same time, possess certain other structural features common to other classes of drugs of abuse (e.g., stimulants).

C. Human vs Nonhuman Investigations

Hallucinogenic agents have been investigated using both human and nonhuman subjects. Only human subjects can accurately assess and describe the subjective effects of these agents. Relatively few hallucinogens have been examined in humans, and even fewer have been examined under the rigorous conditions normally accorded novel therapeutic agents undergoing clinical trials. Legal constraints have discouraged new clinical studies. In addition, some of the currently available data frequently cited in the literature were derived from studies that used small subject populations or that did not examine multiple doses of drug (i.e., complete dose response studies were not conducted). Indeed, some agents that are thought to be inactive have been examined only at relatively low doses; the results of more recent animal studies suggest that such agents might be active in humans if significantly higher doses are examined. Some other problematic studies have involved patients suffering from various mental disorders, and yet other data may be from anecdotal reports. Investigations involving nonhuman subjects are much more common and allow the examination of greater numbers of agents in large numbers of subjects, using multiple doses of drug and carefully controlled conditions. However, there are obvious limitations to this approach, the most prominent being that it is unknown if animals experience subjective effects identical to those experienced by humans; that is, do animals hallucinate? Thus, investigations in this field are fraught with a variety of problems, not the least of which is: Do we rely on human data regardless of source or quality, or do we put some faith in the results of animal studies?

Animal studies tend to fall into two categories: investigative or observational studies and interpretive studies. The former simply categorizes the actions of known hallucinogens in animal subjects (e.g., effect on physiological functions and behavior) 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 and study 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 is, ideally, challenged with other hallucinogens, nonhallucinogens, and ultimately with novel agents. Of course, it can never be assured that novel agents identified in this manner will be hallucinogenic until they have been evaluated in human subjects. Nevertheless, robust and reliable animals 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 would likely be investigations involving both types of subjects.

D. Models and Assay Methods for Hallucinogenic Activity

I. Animal Models

Over the years, numerous animals models of hallucinogenic activity, or at least animal assays that might be useful for examining hallucinogenic agents, have been described (reviewed in 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); these models have also been referred to 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 a human counterpart (e.g., exploratory behavior). Assay models are inferential; that is, there need not be a relationship between the animal and human behavior so long as 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 strip in a tissue bath).

Some common explicit animal models include: (1) the serotonin syndrome, (2) the ear-scratch reflex or scratch reflex stereotypy, (3) the head-twitch response, (4) rabbit hyperthermia, (5) limb-flick behavior in cats or limb-jerk in monkeys, (6) the startle reflex, (7) investigatory behavior, (8) disruption of fixed-ratio responding; the so-called hallucinogenic pause, and (9) drug discrimination using animals trained to standard hallucinogens (reviewed in GLENNON 1992). Combinations of these and other assays have been employed as test batteries (e.g., see OTIS et al. 1978; STOFF et al. 1978) with the hope that a combination of tests might prove more reliable than

any single animal model. 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, animal models have significantly enhanced our understanding of hallucinogenic agents. They have allowed, for example, the formulation and evaluation of a multitude of hypotheses, and there are instances in which novel agents have been found active in animal models and only later have the results been verified in humans. 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).

A major problem that has haunted animal models of hallucinogenic activity/potency is the existence of what have been termed *enigmatic agents*. Certain agents are continually identified by various animal models as being "active" when in fact there is little (or no) supporting human data. These enigmatic 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 are generally 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 or nonexistent; 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 are truly without hallucinogenic effects. Nevertheless, these agents should continue to be used in future studies with animals in order to challenge new models and also to gain additional insight into the agents themselves.

II. Nonanimal Models

Nonanimal techniques have been employed to investigate hallucinogenic agents and, in particular, the structure-activity relationships 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; that is, 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; the approach is amechanistic and simply attempts 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 that have potential mechanistic relevance (e.g., the influence of lipophilicity on receptor affinity for a series of active agents). Although these models may possess some predictive and/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 to be recently explored 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 in WESTKAEMPER and GLENNON 1991). Thus, these models will require validation by empirical methods such as site-directed mutagenesis and/or ligand binding utilizing chimeric receptors. Such studies will be further described in Sect. H.

III. The Drug Discrimination Paradigm

The drug discrimination paradigm (reviewed in GLENNON 1991) was listed above in Sect. D.I along with other animal models of hallucinogenic activity. In fact, it has never been claimed that the paradigm is a model of hallucinogenic activity. Rather, it is a drug detection procedure in which animals that have been trained to discriminate a given training drug from vehicle are essentially asked whether they recognize a novel agent as producing stimulus effects similar to those produced by the training drug. The paradigm is of general applicability and its utility is not limited to the investigation of hallucinogenic agents. Nevertheless, it has proven quite successful in qualitatively and quantitatively identifying hallucinogenic agents. Examples of each major category of classical hallucinogens (with the exception of the β-carbolines) have been used as training drugs in drug discrimination studies, and (+)LSD, 5-OMe DMT, mescaline, 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. Animals trained to one of these agents do not recognize nonclassical hallucinogens such as phencyclidine, opiates, and other agents that may occasionally produce hallucinogenic effects. This is one reason why such agents have been classified under the common heading of classical hallucinogens; and this fact 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 tryptamine hallucinogens, α-emthyltryptamines, ergolines, phenylethylamines, phenylisopropylamines, and β-carbolines have now been

examined. To date, there have been no reports of false negatives, but several false positives have been noted: lisuride and quipazine, but not amphetamine, produce DOM-like stimulus effects. Structure-activity relationships have been formulated, mechanistic studies have been conducted, and for a series of agents (encompassing examples of each category of classical hallucinogens) for which human data are available there is a significant correlation ($r > 0.9$) between discrimination-derived ED50 values and human hallucinogenic potencies (reviewed in GLENNON 1991). It was the use of DOM-trained animals that originally led to the *5-HT_2 hypothesis* of hallucinogen action; this will be further discussed in Sect. F.II.

Another widely used training drug is (+)LSD (e.g., see CUNNINGHAM and APPEL 1987). Although the LSD stimulus generalizes to members of other categories of classical hallucinogens, its stimulus properties may involve multiple neurotransmitter mechanisms including dopaminergic and α_1-adrenergic mechanisms (MEERT et al. 1989; KOEK et al. 1992). False positives have been noted with (+)LSD as training drug. For example, lisuride, quipazine, but not amphetamine, produce (+)LSD-like stimulus effects. Interestingly, however, although animals trained to discriminate (+)LSD from vehicle recognize lisuride, animals can be trained to discriminate (+)LSD from lisuride (CUNNINGHAM and APPEL 1987). These results suggest that lisuride and (+)LSD produce sufficiently common effects to allow them to be recognized by the same animals but sufficiently different effects that allow them to be discriminated.

The actions of DOM, LSD, and structurally related agents, are at least partly related to a 5-HT_2 agonist mechanism (see Sect. F.II). Because there is evidence that 5-HT_2 antagonists may constitute novel classes of antipsychotic agents, antidepressants, and anxiolytics, antagonism of hallucinogen-induced effects in animals is being used to identify new 5-HT_2 antagonists. In particular, the drug discrimination paradigm with animals trained to discriminate various hallucinogens is being increasingly used for this purpose (GLENNON 1991; KOEK et al. 1992; MEERT et al. 1989; MEERT 1991).

E. Structure-Activity Relationships

Structure-activity relationships (SARs) have been formulated for the various classes of classical hallucinogens in order to: (1) determine how structural features influence activity/potency, (2) classify which agents possess membership in the family of agents referred to as classical hallucinogens, and (3) investigate mechanisms of action. Certain hallucinogens have been investigated in greater detail than others. For example, relatively little is known about the ergolines and β-carbolines, whereas much more is known about the indolylalkylamines and phenylalkylamines. The SARs of the latter two categories of agents in producing hallucinogenic activity and in producing activity in various animal models have been described in detail

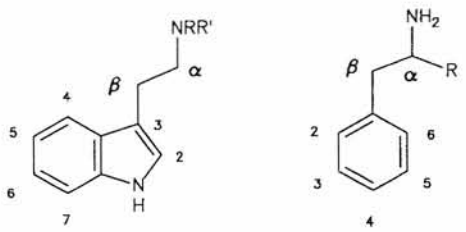


Fig. 2. General structures and numbering system for the indolylalkylamine (*left*) and phenylalkylamine (*right*) classical hallucinogens

(NICHOLS and GLENNON 1984). Where both human and animal data are available, the results are surprisingly consistent. Some of the important and consistent findings will be summarized here. See Fig. 2 for the chemical structures and numbering systems.

I. Indolylalkylamines

Primary amine analogs (i.e., derivatives with unsubstituted terminal amine groups) and most secondary amine analogs (i.e., analogs with one small alkyl substituent) are generally inactive. This may be related to problems associated with their inability to penetrate the blood-brain barrier and/or due to their rapid metabolism. *N,N*-Dialkylamine derivatives are typically active. Derivatives of DMT and DET are the most common in occurrence. Generally, there is little potency difference between DMT analogs and their DET counterparts. Further increasing the size of the alkyl substituents tends to decrease potency. Certain secondary amine analogs (in which the substituent is large enough to enhance lipophilicity or hinder metabolism) are also active.

α-Methyl substitution enhances the potency of primary amine analogs. In general, α-methyl analogs are several times more potent than the corresponding DMT counterparts. Otherwise, the SARs of the α-methyltryptamines seem to parallel those of the *N,N*-dialkyltryptamines. Introduction of the α-methyl group creates a chiral center; that is, two optical isomers are now possible. In the few cases in which individual optical isomers have been examined, the *S*(+) isomers are several times more potent than their *R*(−) enantiomers; nevertheless, both isomers possess activity.

Aromatic substitution can either increase or decrease the potency of DMT and α-methyltryptamine. In general, substitution at the 4- or 5-position by a methoxy group increases potency whereas similar substitution at the 6- or 7-position either decreases potency or abolishes activity. Hydroxylation at the 4-position results in active agents whereas hydroxylation at the 5-, 6-, or 7-positions abolishes activity. Two of the best investigated agents include 4-

OH DMT and 5-OMe DMT. Bufotenine (5-OH DMT or *N*,*N*-dimethyl 5-HT) has been reported to be both hallucinogenic and nonhallucinogenic; for a recent brief review, see MCCLEOD and SITARAM (1985).

II. Phenylalkylamines

Although very few nonprimary amine analogs have been investigated in humans, in general the primary amines are more potent than their corresponding secondary or tertiary amines. In animal studies, even N-monomethylation can decrease potency by an order of magnitude.

α-Methyl-substituted derivatives (i.e., phenylisopropylamines) are usually two to ten times more potent than their corresponding unsubstituted counterparts (i.e., phenylethylamines). As with the indolylalkylamines, this may be related to a greater difficulty in penetrating the blood-brain barrier by, or to more rapid metabolism of, the phenylethylamines. With the phenylisopropylamines, the *R*(−) isomers are usually several-fold more potent than their *S*(+) enantiomers. Thus, whereas stereochemistry seems to play only a small role, the enantioselectivity for indolylalkylamine hallucinogens and phenylisopropylamine hallucinogens is reversed.

Aromatic substitutents have a very significant effect on activity. In the phenylisopropylamine series, in which the terminal amine and aromatic ring are unsubstituted, the agent (i.e., amphetamine) is inactive as a hallucinogen. Monomethoxy substitution typically results in agents that are not hallucinogenic, although these agents are not necessarily centrally inactive. Dimethoxy substitution can result in hallucinogenic agents depending upon the position of the methoxy groups. The best investigated of these is the 2,5-dimethoxy analog (2,5-DMA). The 2,4-DMA may also be active. Of the trimethoxy analogs (TMAs), 2,4,5-TMA is the best investigated. Several of the other possible TMAs are also active. With 2,5-DMA, further substitution at the 4-position leads to the most potent agents. For example, the 4-methyl analog is DOM and the 4-bromo analog is DOB. These general SARs are consistent with those of the phenylethylamines except, as mentioned above, the phenylethylamines are several-fold less potent than their phenylisopropylamine counterparts. See SHULGIN and SHULGIN (1991) for a comprehensive treatment of the role of substituent effects in the actions of phenylalkylamine hallucinogens in human subjects.

F. Mechanism of Action of Classical Hallucinogens

I. The 5-HT Hypothesis

Shortly after the discovery of the neurotransmitter 5-HT in the late 1940s and the realization that both 5-HT and LSD possess and indolylalkylamine nucleus, it was postulated that hallucinogens might act via a serotonergic

mechanism (reviewed in WOOLLEY 1962). However, the structures of the phenylalkylamine hallucinogens bear a greater structural resemblance to catecholaminergic neurotransmitters such as epinephrine, norepinephrine and dopamine than to 5-HT. Thus, initially, it was not unreasonable to assume that catecholaminergic neurotransmitters might be involved in the actions of the phenylalkylamine hallucinogens. Indeed, even LSD has a profound effect on each of these (and other) neurotransmitter systems. Historically, however, there is little empirical support for involvement of most of these neurotransmitters in the common actions of the classical hallucinogens. In contrast, ever since its discovery, 5-HT has been consistently implicated in the actions of hallucinogens.

With the discovery of two distinct populations of peripheral 5-HT receptors (D receptors and M receptors), controversy arose during the 1950s: Do multiple populations of 5-HT receptors exist in human brain? Do hallucinogens act at a subpopulation of 5-HT receptors? If so, do they act as 5-HT agonists or antagonists? During the 1980s and early 1990s, numerous populations of 5-HT receptors were identified: 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C} (now 5-HT_{2C}), 5-$HT_{1D\alpha}$, 5-$HT_{1D\beta}$, 5-HT_{1E}, 5-HT_{1F}, 5-HT_2 (now 5-HT_{2A}), 5-HT_{2F} (now 5-HT_{2B}), 5-HT_3, and 5-HT_4. Some of the most recently described 5-HT receptors include 5-HT_5 and 5-HT_6. This multitude of 5-HT receptors only served to further confound the issue. 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 also belong to this family, but are linked to a phosphoinositol (PI) second messenger systems. Due to their significant transmembrane sequence homology and due to similarities in second messenger systems, 5-HT_{1C} receptors are now termed 5-HT_{2C} receptors. The originally defined 5-HT_2 receptors are currently referred to as 5-HT_{2A} receptors. For the same reasons, and to fill the gap between 5-HT_{2A} and 5-HT_{2C}, 5-HT_{2F} receptors were renamed 5-HT_{2B} receptors. Thus, the 5-HT_2 receptor family consists of three distinct subtypes: 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}. In the remainder of this chapter, the term "5-HT_2" will be used in a generic sense, or to refer to the entire family of 5-HT_2 receptors as a class. If specific information is available on a particular population of 5-HT_2 receptor, the more precise subpopulation name will be used. 5-HT_3 receptors are distinct in being ligand-gated ion channel receptors.

II. The 5-HT_2 Hypothesis

The issue now becomes even more complicated: Which population(s) of 5-HT receptors is involved in the actions of classical hallucinogens? Based on the finding that both 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). In support of this hypothesis, the binding of various hallucinogens at different populations of 5-HT receptors using radioligand binding techniques indicated a common affinity only for 5-HT_2, specifically 5-HT_{2A}, receptors (GLENNON et al. 1984). Indolylalkylamine hallucinogens are fairly nonselective and bind with high affinity at multiple populations of 5-HT receptors; ergolines such as LSD are without significant affinity for 5-HT_3 and 5-HT_4 receptors. In contrast, the phenylisopropylamine hallucinogens such as DOM, DOB, and DOI were found to bind rather selectively at 5-HT_{2A} receptors. Furthermore, there was a significant correlation ($r > 0.9$) between 5-HT_{2A} receptor affinity and both discrimination-derived ED_{50} values and human hallucinogenic potencies (reviewed in GLENNON 1990). For the first time, there was now evidence for a *5-HT_2 hypothesis* of hallucinogenic activity.

However, over the years, several serious problems have arisen regarding the 5-HT_2 hypothesis: (1) Do hallucinogens act as 5-HT_2 agonists or antagonists? (2) Are there subpopulations of 5-HT_2 receptors with which hallucinogens might interact differently? It might be noted that the 5-HT_2 hypothesis was first proposed prior to the discovery of 5-HT_{2B} and 5-HT_{2C} receptors. (3) May some other population of 5-HT receptors (instead of 5-HT_2) be involved in the actions of hallucinogens?

On the basis of drug discrimination studies, it was originally suggested that classical hallucinogens act as 5-HT_2 agonists; however, PIERCE and PEROUTKA (1988) challenged this concept, suggesting that hallucinogens, particularly (+)LSD, act as 5-HT_2 antagonists. This issue has been reexamined and it would appear that hallucinogens are *not* 5-HT_2 antagonists: classical hallucinogens are agonists, or at least partial agonists, at 5-HT_2 receptors (reviewed in GLENNON 1990). Certain hallucinogens, including LSD, may possess a low intrinsic activity; thus, when administered in combination with a full agonist, such agents might occasionally appear to behave as antagonists in some pharmacological assays. However, there is no evidence that 5-HT_2 antagonists (a number of which are currently in clinical trials) such as ketanserin, ritanserin, risperidone, and others produce hallucinogenic effects in humans.

Is it possible that subpopulations of 5-HT_2 receptors exist? In the *two-state hypothesis*, LYON et al. (1987) proposed that 5-HT_2 (now 5-HT_{2A}) receptors exist in two affinity states: a low-affinity state and an agonist high-affinity state. [^{3}H]Ketanserin, a 5-HT_2 antagonist, labels both states of the receptor. Yet the high-affinity state represents only 5%–20% of the binding. By analogy to the adrenergic system, a radiolabeled agonist ligand should label predominantly the high-affinity state of the receptor. Consequently, in an attempt to identify a candidate agonist for labeling, SAR investigation was conducted with DOB. The contribution of each structural feature of DOB to binding was examined and additional analogs were prepared. With the exception of the iodo derivative DOI, no analog was found to bind with higher affinity than DOB, and, at the same time, retain agonist character as

measured using the drug discrimination paradigm. Subsequently, [^{3}H]DOB was synthesized and used as a radioligand in binding studies. Although antagonists were found to bind with comparable affinity at [^{3}H]ketanserin- and [^{3}H]DOB-labeled 5-HT$_2$ sites, agonists were shown to bind with upwards of 50-fold higher affinity at [^{3}H]DOB- vs [^{3}H]ketanserin-labeled sites. 5-HT, for example, binds with 100-fold higher affinity and R(−)DOB with 60-fold higher affinity at [^{3}H]DOB- vs [^{3}H]ketanserin-labeled sites. Thus, it was proposed that [^{3}H]DOB labels the high-affinity (i.e., 5-HT$_{2H}$) agonist state of 5-HT$_2$ receptors (reviewed in GLENNON 1990). Certain DOB analogs which were found to bind with higher affinity than DOB at [^{3}H]ketanserin-labeled sites, but which lacked agonist activity in the drug discrimination paradigm, were subsequently shown to possess nearly identical affinity, but not enhanced affinity, for [^{3}H]DOB-labeled sites. One such example is the 4-(3-phenylpropyl) analog of 2,5-DMA (DOPP). Based on the fact that DOPP binds with similar affinity at [^{3}H]ketanserin- and [^{3}H]DOB-labeled sites (K_i = 10 and 17 n*M*, respectively), it would seem likely that DOPP is a 5-HT$_2$ antagonist. Indeed, DOPP has been demonstrated to act as an antagonist of 5-HT at 5-HT$_2$ receptors linked to phosphoinositide hydrolysis (GLENNON et al. 1992a).

PIERCE and PEROUTKA (1989) later conducted related investigations using [^{77}Br]DOB and proposed an alternative explanation: two different populations (i.e., subpopulations) of 5-HT$_2$, i.e., 5-HT$_{2A}$, receptors (the *two-site hypothesis*) exist. It was suggested that radiolabeled phenylalkylamines label what they termed 5-HT$_{2A}$ receptors whereas [^{3}H]ketanserin labels 5-HT$_{2B}$ receptors. (These 5-HT$_{2A}$ and 5-HT$_{2B}$ receptors should not be confused with those described in Sect. F.I.) Part of their reasoning was based on the finding that [^{77}Br]DOB-labeled sites are absent in bovine cortex. However, because the extent of [^{3}H]ketanserin binding is lower in bovine tissue than in rat tissue and because 5-HT$_{2H}$ sites represent only a small fraction of this value, it was argued that 5-HT$_{2H}$ binding might not be observed with radioligands of low specific activity. The development of high specificactivity [^{125}I]DOI allowed the identification of 5-HT$_{2H}$ sites in bovine brain (GLENNON et al. 1988; TEITLER et al. 1990). Furthermore, 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 in 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.

III. The 5-HT$_{1C}$ Hypothesis

Finally, there is the issue of involvement of other (or additional) populations of 5-HT receptors in the actions of hallucinogens. Shortly after the 5-HT$_2$

hypothesis was proposed in 1983, PAZOS and coworkers (1984) described their discovery of 5-HT_{1C} receptors. Like 5-HT_2 receptors, 5-HT_{1C} receptors are linked to a phosphoinositol second messenger system. Furthermore, both receptors have now been cloned, and within the transmembrane domains there is about an 80% amino acid sequence homology (WEINSHANK et al. 1992). To underscore the similarity between these two types of receptors, they have been recently renamed 5-HT_{2A} and 5-HT_{2C} receptors. A reexamination of the binding of hallucinogens at these receptors found little difference between their 5-HT_2 and 5-HT_{1C} (now 5-HT_{2A} and 5-HT_{2C}) affinities (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. 1992b). As with 5-HT_{2A} receptor affinities, 5-HT_{2C} affinities are also correlated both with discrimination-derived ED_{50} values and human hallucinogenic potencies. In addition BURRIS and SANDERS-BUSH (1988) reported that DOM acts as a 5-HT_{2C} 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 more accurately described as 5-HT_{2A}/5-HT_{2C} antagonists. Thus, the likelihood exists that 5-HT_{2A} and/or 5-HT_{2C} receptors are involved in the actions of hallucinogenic agents.

IV. 5-HT_{2A} vs 5-HT_{2C} Receptors

It is quite difficult to ascribe a specific role for 5-HT_{2C} vs 5-HT_{2A} 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_{2A} receptors bind at 5-HT_{2C} receptors. However, there are a few agents that might offer hope in resolving this problem.

1. Studies with Selective Antagonists

The dopamine/5-HT_{1A} antagonist spiperone binds with approximately 500-fold selectivity for 5-HT_{2A} vs 5-HT_{2C} receptors. Attempts to antagonize the stimulus effects of DOM using various doses of spiperone, with the intention that in might be more difficult to antagonize the DOM stimulus if the stimulus was 5-HT_{2C}-mediated, resulted in inconclusive results due to the severe disruptive effects of low doses of spiperone in combination with DOM (GLENNON 1991). However, recent stimulus antagonism studies with a new spiperone-related analog AMI-193, which displays 2000-fold selectivity for 5-HT_{2A} vs 5-HT_{2C} sites, suggest that the stimulus effects of DOM are primarily 5-HT_{2A}-mediated (ISMAIEL et al. 1993). AMI-193 dose dependently antagonized the stimulus effects of DOM without the disruption associated with spiperone (Fig. 3). Although these results point to a 5-HT_{2A}

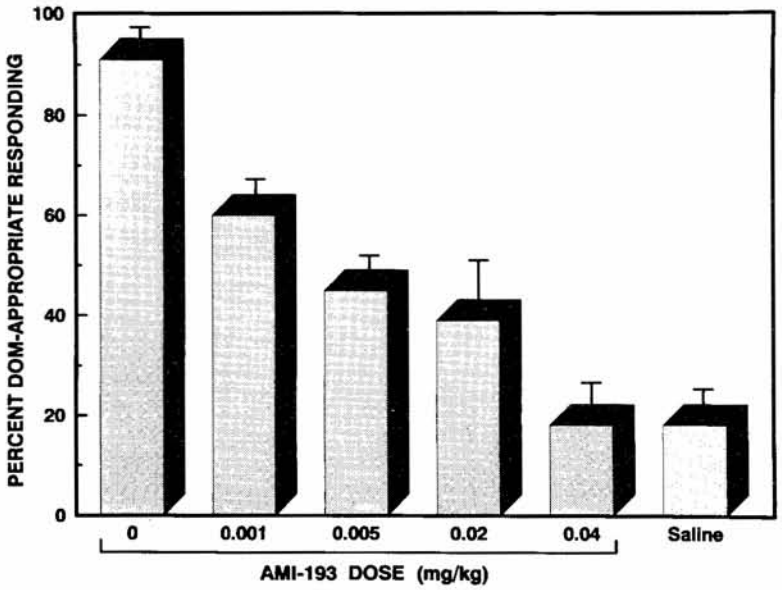


Fig. 3. Antagonism of the DOM stimulus by AMI-193 (ISMAIEL et al. 1993). Doses of AMI-193 were administered 45 min prior to 1.0 mg/kg of the training drug DOM. Saline vehicle, administered alone, produced 18% DOM-appropriate responding

mechanism, a combined 5-HT_{2A}/5-HT_{2C} mechanism cannot be ruled out. That is, if DOM produces a compound stimulus involving both mechanisms, interference with one of the two mechanisms may be sufficient for stimulus antagonism. This problem cannot be satisfactorily resolved until a selective 5-HT_{2C} antagonist has been identified. SCHREIBER et al. (1994) have recently reported that the 5-HT_{2A}-selective antagonist MDL 100,907 or R(+)α-(2,3-dimethoxyphenyl)-1-[2-(4-fluoropheny)ethyl]-4-piperidine-methanol, but not the newly developed 5-HT_{2C}-selective antagonist SB 200,646 or N-(1-methyl-5-indolyl)-N′-(3-pyridyl) urea, is capable of attenuating the stimulus effects of DOI in rats. These findings support earlier suggestions that DOX-type agents, where X = Me, Br, I, act primarily as 5-HT_{2A} agonists in producing their stimulus effects.

2. Studies with Lisuride

SANDERS-BUSH (1994) has recently reported that whereas lisuride is a pure 5-HT_{2C} antagonist, it behaves as a partial agonist at 5-HT_{2A} receptors. The argument has been made that, because lisuride is not hallucinogenic, if hallucinogens act via a 5-HT_{2A} mechanism, they are probably *not* acting as 5-HT_{2A} agonists (SANDERS-BUSH 1994). This argument is not without merit and raises serious questions concerning the 5-HT_2 hypothesis. However, lisuride is one of the enigmatic agents that has been shown to be active in

animal models (e.g., GLENNON 1992; WHITE 1986) and for which there is some evidence of hallucinogenic activity in humans. Most human reports have come from patients who have been receiving lisuride for the treatment of Parkinson's disease; and in at least one case (TODES 1986) the LSD-like effects of lisuride have been argued to involve a dopaminergic rather than serotonergic mechanism (HOROWSKI 1986). However, it is possible that the emetic or other side effects of lisuride preclude use of high enough doses to observe any hallucinogenic effects in normal subjects. Thus, it cannot be argued with any confidence that lisuride is, in fact, a hallucinogen. Interestingly, however, when using rats trained to discriminate DOM from saline, lisuride seems to behave as a partial agonist. That is, at low doses lisuride produces DOM-like stimulus effects; however, given in combination with DOM, lower doses of lisuride attenuate the DOM stimulus effects (GLENNON 1994). Thus, these studies would further argue that the stimulus effects of DOM involve a 5-HT_{2A} mechanism.

3. Studies with TFMPP

1-(3-Trifluoromethylphenyl)piperzine (TFMPP) is a nonselective serotonergic agent that binds at multiple populations of 5-HT receptors. Evidence suggests that TFMPP is a 5-HT_{2C} agonist but a 5-HT_{2A} antagonist (or, at best, a 5-HT_{2A} 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 only in partial generalization, followed, at slightly higher DOM (or DOI) doses, by disruption of behavior. In a third series of experiments, doses of DOM were administered in combination with 0.2 mg/kg of TFMPP (ED_{50} dose = 0.17 mg/kg) to rats trained to discriminate 0.5 mg/kg of TFMPP from vehicle. The rationale was that lower (i.e., nondisruptive) doses of DOM should potentiate the effect of the near ED_{50} dose of TFMPP if both agents act via a common mechanism. The results were somewhat surprising in that low doses of DOM, rather than potentiating the effect, actually antagonized the effect of TFMPP. The results of these studies suggest that DOM and TFMPP produce stimulus effects that are dissimilar. However, a recent report on the complexity of the mechanisms underlying the TFMPP stimulus (HERNDON et al. 1992) make interpretation of these results rather difficult.

4. Radioligand Binding Studies

Although the stimulus effects of DOM may be primarily 5-HT_{2A} mediated, the issue remains as to whether hallucinogens produce their hallucinogenic effects in humans via a 5-HT_{2A} or 5-HT_{2C} mechanism. As mentioned above, human hallucinogenic potency correlates significantly both with 5-HT_{2A} and with 5-HT_{2C} affinity. This issue was recently reexamined (GLENNON and TEITLER, unpublished findings). Using the human potencies published by

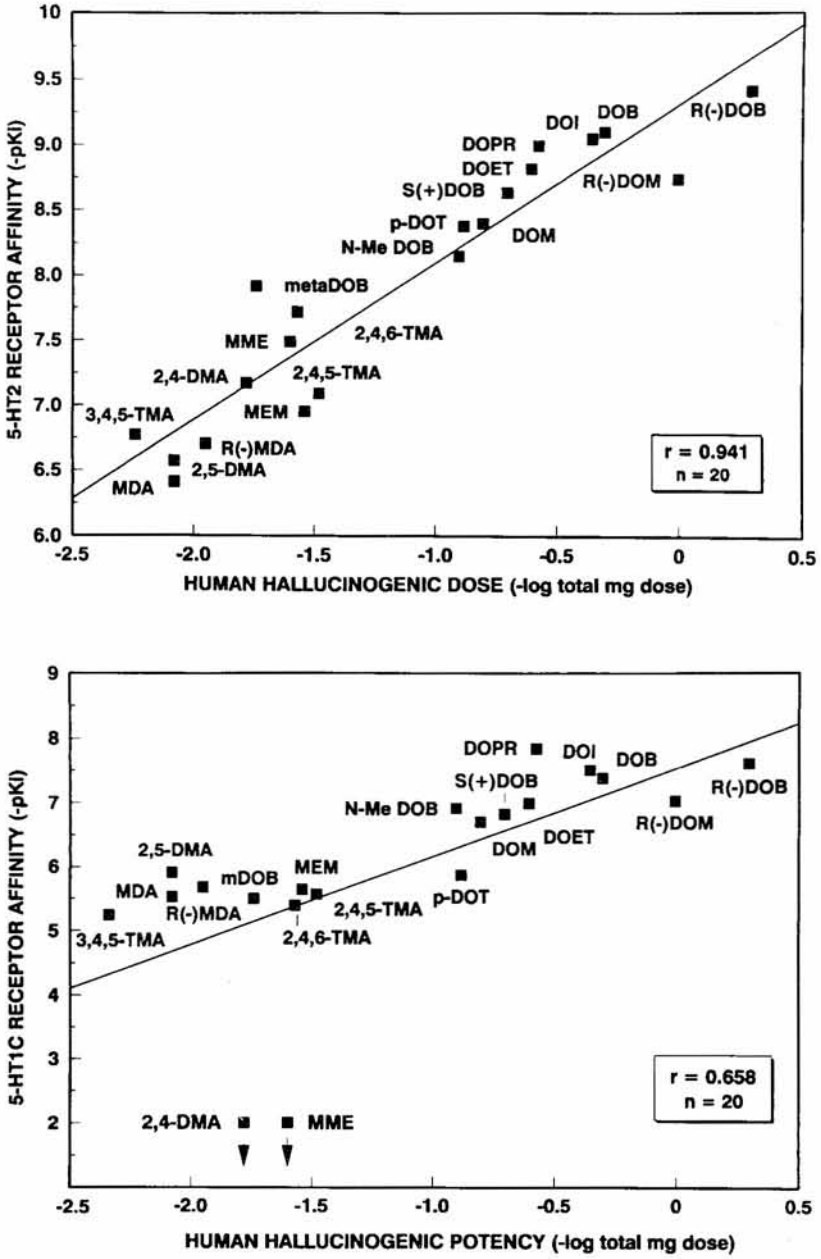


Fig. 4. Relationship between human hallucinogenic potency and 5-HT2 receptor affinity (*upper panel*) and 5-HT1C receptor affinity (*lower panel*) for 20 hallucinogens. Human hallucinogenic potency data are from SHULGIN and SHULGIN (1991)

SHULGIN and SHULGIN (1991), human potency (arithmetic means were used where dose ranges were cited) was found to correlate significantly (r = 0.941; n = 20) with 5-HT_{2A} receptor affinity (Fig. 4). Potency is also highly correlated with 5-HT_{2C} affinity (r = 0.886; n = 18) if two agents (i.e., 2,4-DMA and MME) are deleted from the correlation. However, if all 20 agents are included in the latter correlation, the correlation coefficient drops to r = 0.658 (Fig. 4). That is, there appears to be a better correlation between human potency and 5-HT_{2A} binding data than with 5-HT_{2C} binding data. It should be noted, however, as described above (Sect. C), that some human studies have not examined multiple doses of drug and/or have not involved large subject populations. Unfortunately, 2,4-DMA and MME are among such agents. Therefore, while these results are intriguing, and provide leads for future studies, additional investigation is certainly warranted. At this time, it cannot be concluded that human hallucinogenic activity involves a 5-HT_{2A} rather than, or in addition to, a 5-HT_{2C} mechanism. The existence of a third member of the 5-HT_2 family, 5-HT_{2B} receptors, further confounds this issue. Recent studies (NELSON et al. 1994) have shown that although they display higher affinity for 5-HT_{2A} and 5-HT_{2C} receptors, hallucinogens nonetheless bind at human 5-HT_{2B} receptors. Furthermore, for 17 agents, there was a significant ($r > 0.9$) correlation between 5-HT_{2B} affinity and both 5-HT_{2A} and 5-HT_{2C} affinity.

V. Involvement of Other 5-HT Receptors

We and others have 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 in GLENNON et al. 1991). 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 5-HT receptors. For instance, indolylalkylamine hallucinogens are nonselective serotonergic agents. What is the effect of a nonselective agonist that can interact 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 at another? Experiments necessary to sort out these types of interactions could be rather labor intensive and their interpretation quite complicated. Nonetheless, this, too, offers direction for future work. For example, it is possible that the nonselective nature of certain agents (e.g., 5-HT, administered as such or as the 5-HT precursor tryptophan) that can interact at multiple populations of 5-HT receptors results in the agents being nonhallucinogenic because they can "turn off" certain receptor-mediated events that might have otherwise resulted in hallucinogenic activity. Do some of the enigmatic agents act in a similar manner? That is, enigmatic agents may give false positives in a particular animal model or assay that primarily involves only a single receptor popula-

tion (e.g., radioligand binding); but in other instances, in which multiple populations of receptors are present, interaction of these nonselective agents at various populations may modulate or abolish this effect and the agents might appear inactive.

The DOM stimulus does not generalize to the 5-HT_{1A} agonist 8-OH DPAT nor does an 8-OH DPAT stimulus 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, we have 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 ED50 dose of DOM behave as if they have received the training dose of DOM (i.e., stimulus generalization occurs upon administration of the ED_{50} dose of DOM) (see inset, Fig. 5). Furthermore, pretreatment of animals with 0.05 mg/kg of 8-OH DPAT results in a leftward shift of the DOM dose-response curve (Fig. 5). 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.

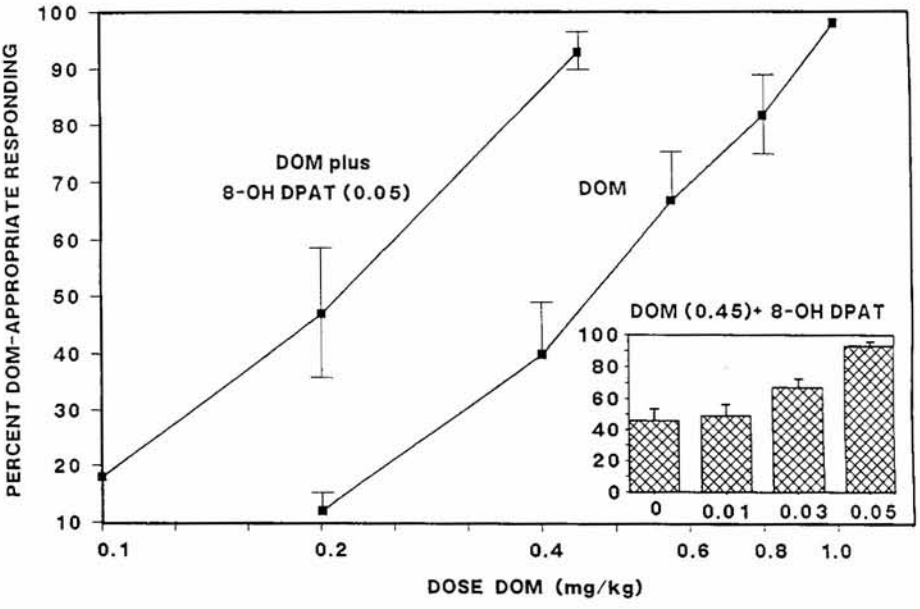


Fig. 5. Effect of the 5-HT1A agonist 8-OH DPAT in combination with training drug DOM (1 mg/kg) in rats trained to discriminate DOM from saline. Dose-response curve for DOM (*right*) and for DOM in animals pretreated with 0.05 mg/kg of 8-OH DPAT (*left*). *Inset* shows effect of different doses of 8-OH DPAT administered combination with the ED_{50} dose (0.45 mg/kg) of DOM. Data previously reported (GLENNON 1991)

Similar studies have been conducted with 5-HT_3 agents (GLENNON 1994). 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% DOM-appropriate responding; higher doses appear to have less of an attenuating effect. The 5-HT_3 (partial) agonist metachlorophenylbiguanide (mCPBG) also has an unusual effect on the DOM stimulus. 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 (higher doses producing disruption of behavior). We have conducted parallel studies using rats trained to discriminate the structurally related agent 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%. The effect of mCPBG is not unlike that seen with DOM. The results suggest a possible modulatory effect by 5-HT_3 receptors on the DOM and MDMA stimuli. (It might be noted, for purpose of comparison, that zacopride has 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.

VI. Involvement of Dopamine Receptors

There is no question that LSD can influence dopaminergic function (e.g., CUNNINGHAM and APPEL 1987; WHITE 1986). In fact, the hallucinogenic effects of LSD may involve, at least in part, a dopaminergic mechanism. To date, however, there is little to no evidence that dopamine plays a significant role in the actions of simple tryptamine or phenylalkylamine hallucinogens. It may be the added effect on dopamine (or other neurotransmitter) receptors that accounts for the unusually high potency and unique effects of LSD relative to some of the other classical hallucinogens. A role for dopamine receptors in the actions of these agents requires further investigation. It should be noted, however, that examples of many different classes of dopamine antagonists bind with high affinity at 5-HT_{2A} and 5-HT_{2C} receptors (ROTH et al. 1992). Thus, blockade of the effect of a hallucinogen by one of these agents cannot necessarily be taken as reliable support for involvement of a dopaminergic mechanism. 5-HT_3 ligands also appear to indirectly modulate the effect of dopamine (COSTALL et al. 1990; KILPATRICK et al. 1990). This might explain some of the effects noted above when 5-HT_3 antagonists were administered in combination with DOM in drug discrimination studies. In contrast, however, 5-HT_3 antagonists had essentially no effect on the stimulus properties of (+)amphetamine – an agent thought to

produce its stimulus effects primarily via a dopaminergic mechanism (YOUNG and GLENNON 1986).

G. Structurally Related Agents and Designer Drugs

The phenylisopropylamine stimulant amphetamine and phenylisopropylamine hallucinogens such as DOM or DOB (Fig. 1) produce effects in animals and in human subjects that are clearly distinguishable from one another (SHULGIN and SHULGIN 1991). Thus phenylisopropylamines can be divided into at least two distinct classes of psychoactive agents. Structure-activity studies reveal which various substituents influence potency and, occasionally, how they do so. However, as the structure of one of these agents is gradually modified to one of the others, at what point does an amphetamine-like agent become, for example, a hallucinogenic agent? This question is especially pertinent to the investigation of designer drugs, which are agents that share a structural similarity with phenylisopropylamine stimulants and phenylisopropylamine hallucinogens. The α-desmethyl analog of DOB, Nexus, is an example of an agent that seems to retain much of the hallucinogenic character of DOB. Cathinone (or β-ketoamphetamine) and methcathinone (*N*-methylcathinone) are newly scheduled agents that possess amphetamine-like properties. Are there structures that possess both properties? Is some of the appeal of designer drugs related to a combination of stimulant and hallucinogenic effects? For a review of designer drugs, see ASGHAR and DESOUZA (1989).

It has been said that 1-(3,4-methylenedioxyphenyl)-2-aminopropane (MDA; Fig. 6) produces effects in humans that are akin to a combination of cocaine and LSD. It would seem then that MDA is capable of producing both amphetamine-like and hallucinogenic effects. In tests of stimulus generalization with groups of rats trained to discriminate (+)amphetamine

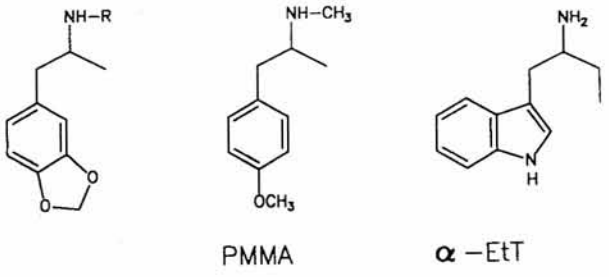


Fig. 6. Chemical structures of several designer drugs and related agents: 1-(3,4-methylenedioxyphenyl)-2-aminopropane (MDA) and its N-monomethyl and N-monoethyl derivatives MDMA and MDE (where R = -H, $-CH_3$, and $-C_2H_5$, respectively), *N*-methyl-1-(4-methoxyphenyl)-2-aminopropane (*PMMA*), and α-ethyltryptamine (*α-EtT*)

from vehicle and DOM from vehicle, it has been demonstrated that MDA produces both amphetamine-like and DOM-like effects. The amphetamine-like effect rests primarily with the *S*(+)isomer, whereas the *R*(−)isomer of MDA is the more DOM-like. Rats trained to discriminate MDA from vehicle recognize (+)amphetamine, cocaine, DOM, and LSD. Furthermore, rats can be trained to discriminate 1.25 mg/kg of *S*(+)MDA from 1.25 mg/kg of *R*(−)MDA from saline vehicle using a three-lever operant paradigm (YOUNG and GLENNON 1992), suggesting that the stimulus effects of the isomers of MDA are distinguishable from one another. Furthermore, upon administration of (+)amphetamine, the animals respond in a dose-related fashion on the *S*(+)MDA-appropriate lever, whereas after administration of DOM responding is on the *R*(−)MDA-appropriate lever. Thus, although amphetamine, DOM, and MDA all possess a common phenylisopropylamine skeleton, their actions differ; MDA seems to produce effects similar both to amphetamine and DOM. Therefore it seems that substituents do indeed influence activity.

Attempts have been made to classify phenylisopropylamines as being either amphetamine-like or DOM-like using drug discrimination. Numerous such agents have been already classified (GLENNON 1991, 1993a). Interestingly, certain phenylisopropylamines produce neither amphetamine-like nor DOM-like stimulus effects, and yet they produce MDA-like effects. 1-(3,4-Dimethoxyphenyl)-2-aminopropane (3,4-DMA), and *N*-ethyl MDA (MDE; "Eve," Fig. 6) are examples of such agents. *N*-Ethyl MDA is a chain-extended analog of the designer drug *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane (MDMA) ("Ecstasy," "Adam," Fig. 6). MDMA produces amphetamine-like, but not DOM-like, stimulus effects. Such agents might be capable of producing a unique behavioral effect that is distinct from that of the phenylisopropylamine stimulants and hallucinogens (NICHOLS and OBERLENDER 1989). Initially it was thought that this property might be a consequence of the methylenedioxy group which is present in MDA, MDMA, MDE, and related agents. However, other agents that lack the methylenedioxy group produce MDMA-like effects in animals trained to discriminate MDMA from vehicle. Examples of such agents include paramethoxymethamphetamine (PMMA) (GLENNON and HIGGS 1992) and 1-(3-methoxy-4-methylphenyl)-2-aminopropane (JOHNSON et al. 1991). It would appear then that psychoactive phenylisopropylamines can be divided into at least three categories: (1) stimulants, (2) hallucinogens, and (3) MDMA-like agents. The MDMA-like agents may occasionally retain varying degrees of central stimulant or hallucinogenic activity, but, at least on the basis of drug discrimination studies, it would seem that certain of these agents lack such effects and produce what might be an altogether different psychoactive effect. This poorly understood third category of agents has been extensively investigated by NICHOLS and coworkers (e.g., NICHOLS and OBERLENDER 1989). They have identified several novel agents that lack stimulant and hallucinogen-like effects but that, at the same time, retain MDMA-like effects.

Now that it is realized that a methylenedioxy group is no longer required for MDMA-like activity, there is no reason why investigations must be limited to such derivatives. In fact, there is now evidence that indolylalkylamine derivatives may possess MDMA-like character. For example, α-ethyltryptamine (α-EtT, Fig. 6), a homolog of the hallucinogen α-MeT, is a pyschoactive agent that has defied categorization. Although it was first studied in the early 1960s, and although it has been shown to produce some LSD-like effects in humans (MURPHREE et al. 1961), it has never been classified as a simple hallucinogenic agent. α-EtT has recently appeared on the illicit market as a new designer drug ("ET"), and anecdotal reports suggest that it produces effects similar to MDMA. Studies with MDMA-trained rats have now demonstrated that α-EtT, but not α-MeT, does in fact result in MDMA-stimulus generalization (GLENNON, 1993).

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 which agents produce which effects.

H. Molecular Modeling of Hallucinogen-Receptor Interactions

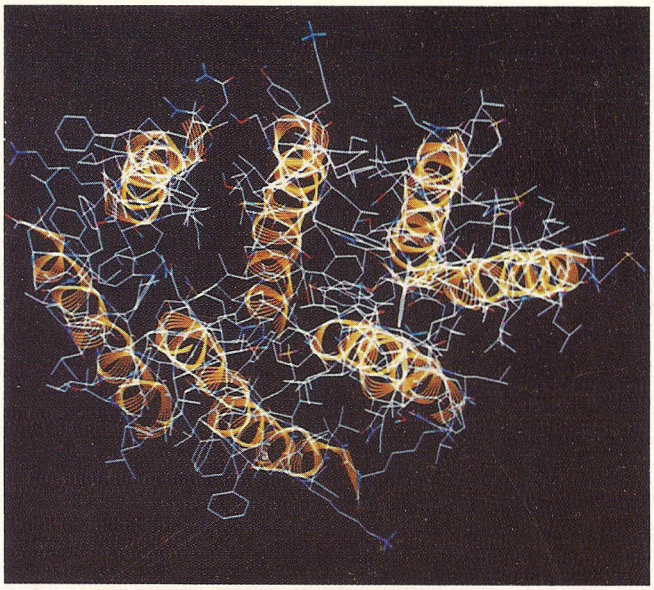
Although the exact mechanism of action of classical hallucinogens is unknown at this time, current evidence supports the contention that 5-HT_{2A} and/or 5-HT_{2C} receptors may be involved. This effect may be further modulated by 5-HT_3, dopamine, or some other receptor(s). In order to design specific hallucinogen antagonists, to be able to predict the hallucinogenic liability of new therapeutic agents, or simply to unravel the mysteries of neurotransmitter receptors, it would be profitable to have some understanding of how hallucinogen-receptor interactions take place. The ideal situation would be to obtain an X-ray crystal structure of a hallucinogen-bound receptor. Assuming that hallucinogens act as 5-HT_{2A} or 5-HT_{2C} agonists, the target would be an X-ray crystal structure of one of these two receptors. Then, once it is realized which amino acid residues are important for binding, it should be possible to identify what other drugs would utilize these same residues; such agents would likely act either as hallucinogens or as hallucinogen antagonists. Subsequent drug design could be conducted at a molecular level.

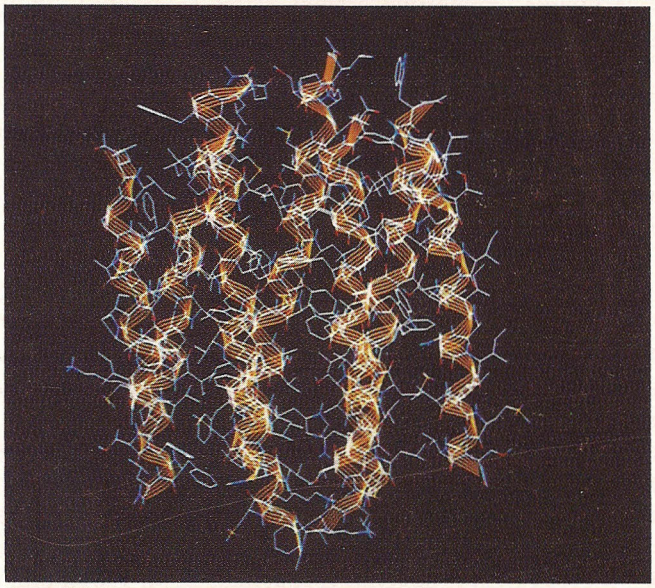
The most significant flaw in the above scenario is that, to date, no crystal structure has ever been reported for a membrane-bound G-protein-coupled neurotransmitter receptor. However, several 5-HT receptors, including human 5-HT_{2A} and 5-HT_{2C} receptors (SALTZMAN et al. 1991), have now been cloned and their sequences made available. Also, the three-dimensional structure of the light-sensitive proton pump from bacteria, bacteriorhodopsin, has been determined to near atomic resolution. Although this is not a G-protein receptor, and although there is a low degree of

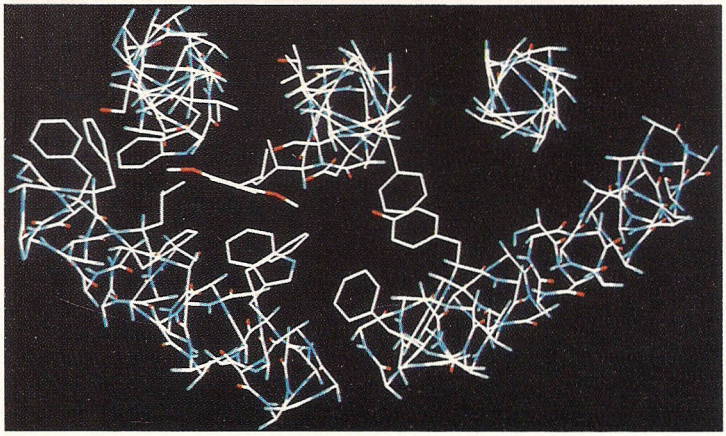
sequence homology between the structures of bacteriorhodopsin and G-protein coupled receptors, it might be possible to deduce structures of neurotransmitter receptors from that of bacteriorhodopsin using molecular modeling techniques. Several investigators are now taking this, or a related, approach to investigate 5-HT_{2A} and 5-HT_{2C} receptors (e.g., EDVARDSEN et al. 1992; TRUMPP-KALLMEYER et al. 1991; WESTKAEMPER and GLENNON 1992, 1994; ZHANG and WEINSTEIN 1993). Bacteriorhodopsin consists of seven membrane-spanning α-helices connected by intracellular and extracellular loops. By analogy, the neurotransmitter receptors may form a similar arrangement whereby the seven helices form a pore in which drugs can bind. Theoretically, there are a number of different solutions to this problem; that is, a drug can hypothetically interact in more than one orientation with the various receptor features. Proposed binding modes can be tested and validated to some extent by the results of site-directed mutagenesis. That is, if a specific receptor feature is proposed to be important for the binding of a particular agent, a synthetically mutated receptor lacking this feature should display reduced affinity for this agent. Such studies are currently in progress in a number of different laboratories.

Specifically, with regard to a hallucinogen-5-HT_2 receptor interaction, it has been proposed that the terminal amine of classical hallucinogens interacts with the asparate moiety in transmembrane helix III (WESTAKAEMPER and GLENNON 1992, 1994). Other important structural features of the hallucinogens, such as aromatic rings and aryl substituents, interact with other amino acid residues on several of the other helices. One such hypothetical model showing the interaction of $R(-)$DOB with a 5-HT_{2A} receptor is presented in Fig. 7. Since DOB, for example, also interacts with 5-HT_{2C} receptors but not with 5-HT_{1A} receptors, binding features in the 5-HT_{2A} model should also be found in a 5-HT_{2C} receptor model but should be absent in a 5-HT_{1A} receptor model. It should be emphasized that this is only one of several possible models; additional studies are necessary to further support this hypothesis vs other possible modes of binding. Nevertheless, these are the first steps in an entirely novel approach to the investigation of hallucinogen-receptor interactions.

Fig. 7. Model of 5-HT2 receptors. The *top* and *middle portions* of the figure represent a top (extracellular) and side view, respectively, of a 5-HT2 receptor model. The ribbons denote the helical backbone structures and helix numbering begins from the right most helix (as transmembrane helix 1) and proceeds in a counterclockwise manner. The *bottom portion* of the figure shows a hypothetical mode of interaction of $R(-)$DOB with the 5-HT2 receptor as viewed from the extracellular side. (From WESTKAEMPER and GLENNON 1992).







I. Summary

Classical hallucinogens consist of a large number of structurally related indolylalkylamine and phenylalkylamine derivatives that produce preceptural alterations in humans. Certain indolylalkylamines (e.g., DMT, 5-OMe DMT, psilocin) and phenylalkylamines (e.g., mescaline) are naturally occurring, but most are synthetic derivatives. Although the effects produced by these agents may not be identical, many seem to share some behavioral similarity. The results of drug discrimination studies, particularly those with DOM as training drug, support this suggestion. And yet the effects of specific agents can also be rather different (see SHULGIN and SHULGIN 1991). In the absence of comprehensive clinical data, various animal models and behavioral assays have been developed to study these agents. While such studies allow for detailed and comparative investigations of large numbers of agents, in some instances animal studies may be a poor substitute for clinical studies when examining drugs whose primary effect in humans is subjective in nature. Nevertheless, numerous animal assay techniques, though not foolproof, have provided an enormous amount of information that would have been otherwise lacking. Indeed, where both human and animal data are available, SARs, for example, have been remarkably consistent. Animal studies have also implicated a role for 5-HT_{2A} and/or 5-HT_{2C} receptors as mediating the effects that classical hallucinogens have in common. Other neurotransmitters may also play a role in their actions, or at least in the actions of some of the agents; but, convincing evidence has yet to be obtained and additional studies are required.

Structurally, the phenylisopropylamine hallucinogens are derivatives of amphetamine. However, these hallucinogens typically lack amphetamine-like stimulant properties. Conversely, amphetamine is not a hallucinogen. Certain phenylisopropylamine designer drugs and related agents are hallucinogenic, some are amphetamine-like, and yet others are both. Some agents produce a unique nonhallucinogenic nonamphetamine effect. Depending upon the presence and nature of substituent groups, phenylisopropylamine derivatives can produce a combination of these effects. Likewise, some indolylalkylamines are hallucinogenic; some, such as α-MeT, are hallucinogenic with stimulant properties (MURPHREE et al. 1961), and at least one, α-EtT, can produce MDMA-like effects.

Finally, apart from any drug abuse-related issues, classical hallucinogens are proving to be useful neurochemical tools. For example, [^{3}H]DOB, [^{77}Br]DOB, [^{125}I]DOI, and [^{3}H]LSD have found application in radioligand binding and autoradiographic studies for labeling 5-HT_{2A}, 5-HT_{2C} and other receptors. MDMA and its analogs have prompted investigations of neurotoxicity. Various animal assays are being used with the idea that antagonism of hallucinogen-induced effects may identify novel psychotherapeutic agents. Clearly, the classical hallucinogens and their structural relatives are an interesting, yet complex, group of agents.

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