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Discriminative Stimulus Properties of Hallucinogens and Related Designer Drugs

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CLASSICAL HALLUCINOGENS

Hallucinogenic agents are of several categories (see table 1). The present review considers only those agents referred to as classical hallucinogens and certain structurally related designer drugs. Most of the nonclassical hallucinogens are treated separately elsewhere. The stimulus properties of the classical hallucinogens have been previously reviewed (Glennon et al. 1982, 1983*a*).

Nature of the Stimulus

Several examples of hallucinogens have been widely used as training drugs in drug discrimination (DD) studies. These include the simple tryptamine 5-methoxy-N,N-dimethyltryptamine (5-OMe DMT), the ergoline (+)lysergic acid diethylamide (LSD), the phenethylamine mescaline, and the phenylisopropylamine 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) (Glennon et al. 1983*a*). Stimulus generalization occurs between these four agents regardless of which is used as the training drug. This is part of the justification for treating the classical hallucinogens as a group. On the other hand, stimulus generalization does not typically occur between the classical hallucinogens and the nonclassical hallucinogens, regardless of which is used as the training drug. Indeed, the classical hallucinogens appear to share a common mechanism of action, whereas (1) their mechanism of action seems to be different from that of the nonclassical hallucinogens, and (2) each type of nonclassical hallucinogen probably possesses its own distinct mechanism of action. Also the DD procedure of using animals trained to discriminate a classical hallucinogen from saline does not represent an animal model of hallucinogenic activity (Glennon 1991). Stimulus effects of the classical hallucinogens involve, at least in part, a mechanism of serotonin (5-HT); thus,

TABLE 1. *Classification of hallucinogenic agents*

Classical Hallucinogens
Indolealkylamine hallucinogens
Simple tryptamine (e.g., DMT, 5-OMe DMT, psilocin)
α-Methyltryptamines (e.g., α-MeT, 5-OMe α-MeT)
β-Carbolines (e.g., harmine, harmaline, 6-OMe harmalan)
Ergolines (e.g., (+)LSD, other lysergic acid analogs)
Phenalkylamines
Phenethylamines (e.g., mescaline)
Phenylisopropylamines (e.g., DOM, DOB, certain DMAs and TMAs)
Other Hallucinogens/Psychotomimetics
Cannabinoids
Phencyclidine (PCP)-related agents
Certain opiates
Certain cholinergic agents
Miscellaneous

stimulus generalization may occur between a classical hallucinogen stimulus and stimuli produced by, for example, nonhallucinogenic agents capable of acting as direct or indirect 5-HT agonists. For example, an LSD stimulus and/or DOM stimulus generalizes with the 5-HT-releasing agent fenfluramine and the nonselective 5-HT agonist quipazine. Both the LSD stimulus and the DOM stimulus generalize to the nonselective 5-HT/dopamine (DA) agonist lisuride. And yet, animals can be trained to discriminate between LSD and lisuride in a three-lever paradigm (Callahan and Appel 1990). Although the DOM stimulus (1 mg/kg) generalizes to 0.6 mg/kg of lisuride, administration of 0.01 mg/kg of lisuride in combination with the training dose of DOM results in attenuation by 50 percent of the DOM stimulus (see figure 1; higher doses of lisuride in combination with DOM result in disruption of behavior). It appears, then, that lisuride may be a partial agonist, and Colpaert et al. (1982) have indeed shown that at sufficiently high doses a variety of 5-HT "antagonists" can in fact mimic the LSD stimulus, suggesting that they too may be acting as partial agonists.

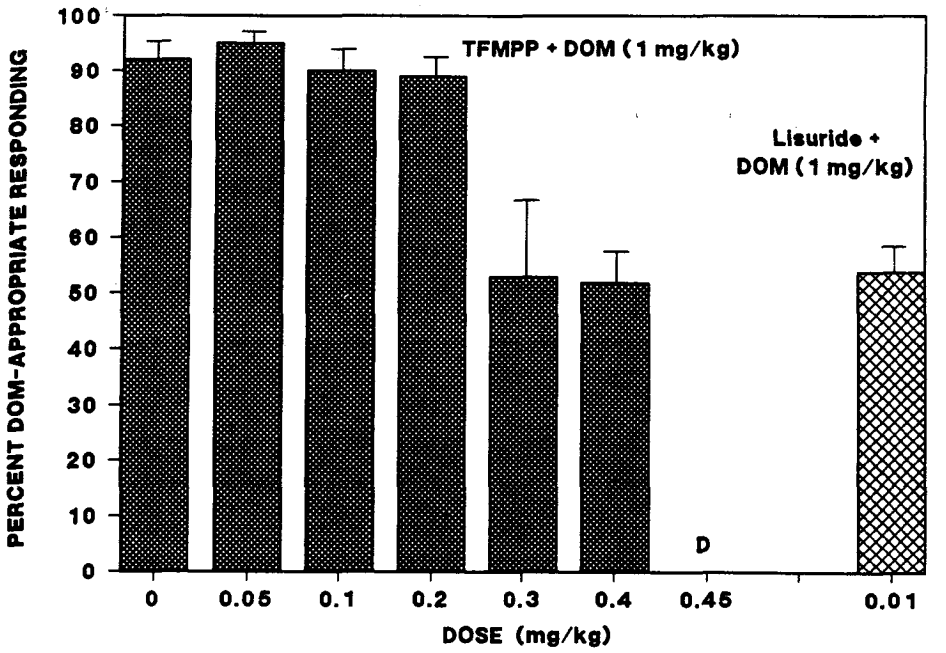


FIGURE 1. *Effect of TFMPP and lisuride administered in combination with DOM in rats trained to discriminate 1 mg/kg of DOM from saline. Doses of TFMPP and lisuride greater than 0.4 and 0.01 mg/kg, respectively, in combination with DOM result in disruption of behavior.*

5-OMe DMT and LSD may produce their stimulus effects via a multiple (and perhaps dose-dependent) serotonergic mechanism; DOM seems to produce a more selective stimulus, and R(–)DOB may be even more selective than DOM (Glennon 1988). In addition to any serotonergic involvement, recent work by Meert et al. (1990) suggests that the stimulus effects of LSD involve a catecholaminergic mechanism.

Mechanism of Action

Early studies with LSD, 5-OMe DMT, mescaline, and DOM concluded that these agents act via a 5-HT agonist mechanism. For example, certain 5-HT agonists mimicked the stimulus effects of hallucinogens, whereas known 5-HT antagonists were capable of antagonizing these effects. Curiously, however, the 5-HT antagonist cinanserin was a relatively weak LSD antagonist and was

much more effective in attenuating the stimulus effects of mescaline (Glennon et al. 1983*a*). Initial arguments related these differences to the effectiveness of the hallucinogens as discriminative stimuli. Furthermore, 5-OMe DMT and LSD seemed to produce somewhat different stimulus properties depending on their training dose (Glennon 1988). In addition, although hallucinogen stimuli generalized with some 5-HT agonists, generalization did not occur with certain other 5-HT agonists. These and other studies raised the possibility of some subtle differences between the stimulus effects produced by indolealkylamine hallucinogens and phenalkylamine hallucinogens.

Puzzling as it was at the time, we now know that there are multiple populations of central 5-HT receptors (e.g., 5-HT_1, 5-HT_2, 5-HT_3). In 1983, Glennon et al. (1983*b*) demonstrated that the stimulus effects of DOM, and DOM-stimulus generalization to examples of other categories of classical hallucinogens such as LSD, 5-OMe DMT, and mescaline, were potently antagonized by the 5-HT_2 antagonist ketanserin. Colpaert et al. (1982) had reported 1 year earlier that pirenperone was a specific LSD antagonist; pirenperone is now recognized as a 5-HT_2 antagonist. Other 5-HT_2 antagonists also potently inhibit the DOM stimulus. These findings led to the hypothesis that hallucinogens produce their stimulus effects via a 5-HT_2 agonist mechanism (Glennon et al. 1983*b*). Later, with the use of LSD-trained rats, the LSD stimulus was also potently antagonized by various 5-HT_2 antagonists (for a review see Cunningham and Appel 1988).

On the basis that the DOM stimulus was a "cleaner" cue than that produced by indolealkylamine hallucinogens, detailed mechanistic and structure-activity relationship (SAR) studies were performed using DOM as the training drug. Subsequent studies revealed the following:

- DOM and DOM-related agents such as DOB and DOI are 5-HT_2 agonists (or at least partial agonists).
- Indolealkylamine hallucinogens are nonselective 5-HT_2 agonists (i.e., although they can act as 5-HT_2 agonists, they bind at various subpopulations of 5-HT_1 sites with high affinity and also act as 5-HT_1 agonists).
- Hallucinogen-induced stimuli can be attenuated by a wide variety of 5-HT_2 antagonists.
- DOM-stimulus generalization does not occur with serotonergic agents that are selective for other populations of 5-HT receptors (e.g., the 5-HT_{1A} agonist 8-OH DPAT).

- For a wide variety of hallucinogens, DOM-stimulus generalization potency is significantly correlated with their affinity for central 5-HT_2 receptors (for a review see Glennon et al. 1984).

Stimulus effects produced by DOM are distinct from those produced by the 5-HT_{1A} agonist 8-OH DPAT (Glennon 1988); in fact, in DOM-trained rats, low doses of 8-OH DPAT (e.g., ≤0.1 mg/kg) produce less than 10 percent DOM-appropriate responding. However, because we have recently demonstrated that 5-HT_1 agonists can modulate certain behavioral effects of 5-HT_2 agonists (Glennon et al. 1990), we were interested in determining the effect of 8-OH DPAT on the DOM stimulus. As shown in figure 2, 50 µg/kg produces a shift to the left of the dose-response curve for DOM in DOM-trained animals (ED_{50} = 0.45 vs. 0.19 mg/kg). Apparently 8-OH DPAT can augment the stimulus effects of DOM. This is currently under further investigation.

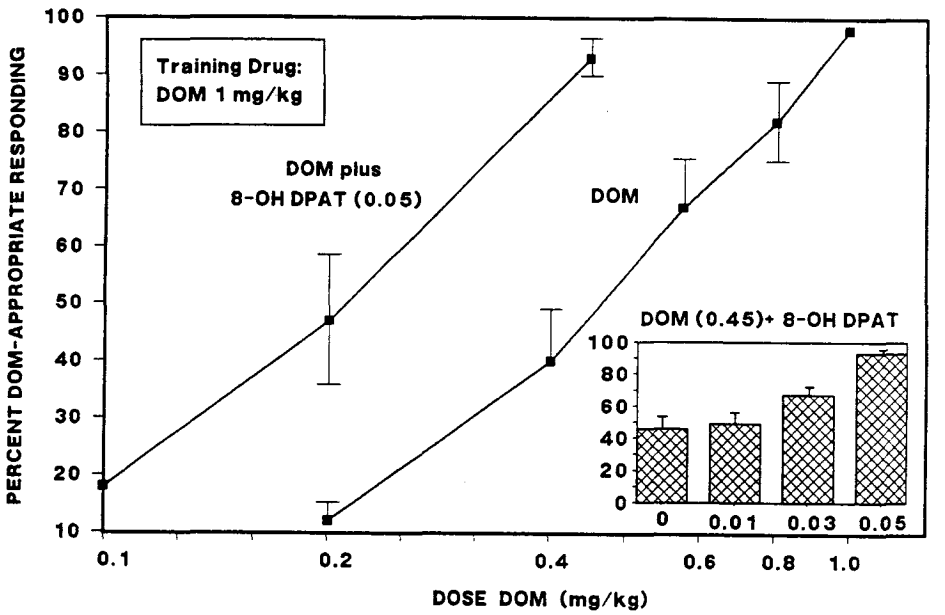


FIGURE 2. *Effect of 50 µg/kg of 8-OH DPAT on the dose-response curve of DOM in DOM-trained rats. 8-OH DPAT was administered 5 min prior to DOM and DOM was administered 15 min prior to testing. Inset shows the effect of different doses of 8-OH DPAT in combination with the ED_{50} dose of DOM.*

Hartig (1989) has demonstrated a significant homology between 5-HT_{1C} and 5-HT_2 receptors. Indeed, although DOM-like agents are quite selective for 5-HT_2 receptors, they also bind (with a tenfold to fiftyfold lower affinity) at 5-HT_{1C} receptors (Titeler et al. 1988). This raises the possibility that the stimulus effects of certain classical hallucinogens may involve a 5-HT_{1C} component. To date, 5-HT_{1C}-selective agents are unavailable to test this hypothesis. 1-(3-trifluoromethylphenyl)piperazine (TFMPP) is a 5-HT_{1B}/5-HT_{1C} agonist; stimulus generalization does not occur between DOM and TFMPP regardless of which is used as the training drug. TFMPP also binds at 5-HT_2 sites, and there is evidence that it may be a 5-HT_2 antagonist. In stimulus antagonism studies using rats trained to discriminate 1 mg/kg of DOM from saline, 0.3 and 0.4 mg/kg of TFMPP attenuate the DOM stimulus by about 50 percent; higher doses (0.45 to 0.7 mg/kg) of TFMPP administered in combination with DOM produce disruption of behavior. Most 5-HT_2 antagonists such as ketanserin are also 5-HT_{1C} antagonists, and their affinities for 5-HT_{1C} receptors and 5-HT_2 receptors are rather similar. The one exception is the DA antagonist spiperone; this agent is a more effective 5-HT_2 antagonist than a 5-HT_{1C} antagonist. Tests of stimulus antagonism were conducted with spiperone using DOM-trained rats (figure 3); doses of up to 0.1 mg/kg were without effect and higher doses produced disruption of behavior. Thus, at this time it is not possible to rule out 5-HT_{1C} involvement in the stimulus effects of DOM. It might be noted that because of its DA antagonist actions, spiperone was able to attenuate the stimulus effects of S(+)amphetamine in amphetamine (AMPH)-trained animals.

Because DOM is a phenylisopropylamine, it has been speculated for years that DOM might produce stimulus effects similar to those of the structurally related phenylisopropylamine stimulant AMPH. In fact, it was once thought that DOM, like AMPH, might be acting via a dopaminergic mechanism. However, it has been demonstrated that DOM and AMPH produce distinct stimulus effects regardless of which is used as the training drug. Nevertheless, certain other DOM analogs to which the DOM-stimulus generalizes (i.e., 2,4,5-trimethoxy analog [TMA], 3,4,5-TMA, 2,5-dimethoxy analog [DMA]) produce as much as 46 percent AMPH-appropriate responding in S(+)AMPH-trained animals (Glennon et al. 1985). In fact, these agents may produce some central stimulant effects in humans (Shulgin 1978). As a consequence, we sought to determine if these agents would produce AMPH-like effects in AMPH-trained rats when the 5-HT_2 response was blocked. Tests of stimulus generalization were conducted in S(+)AMPH-trained rats that had been pretreated 45 min earlier with a dose of ketanserin (0.5 mg/kg), which completely attenuates the effect of DOM in

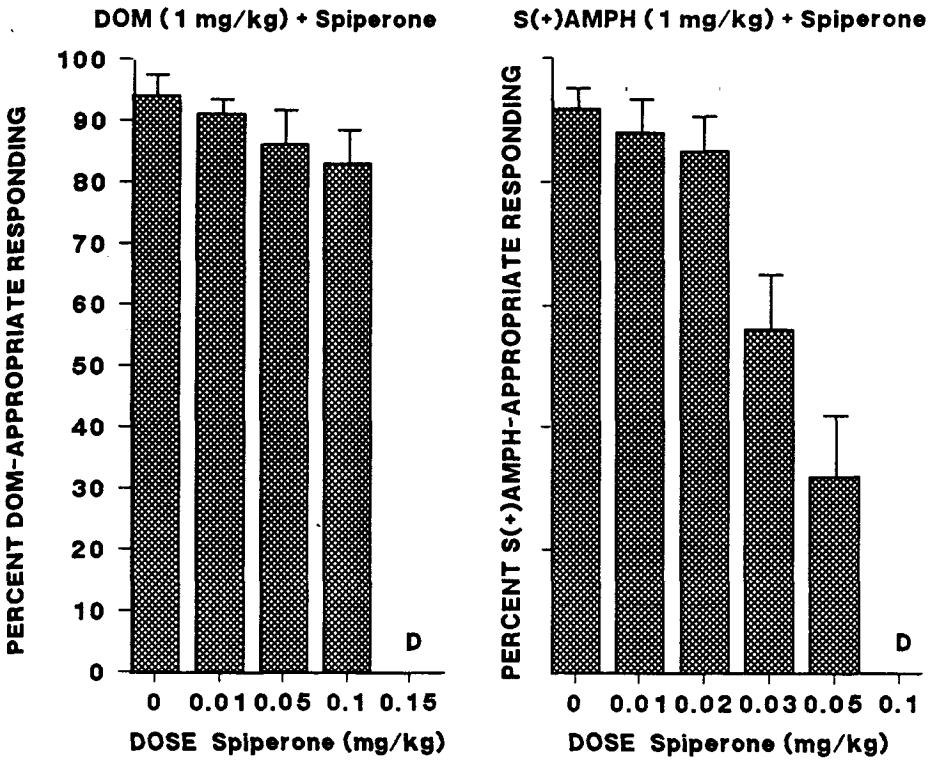


FIGURE 3. *Tests of stimulus antagonism with spiperone in rats trained to discriminate either 1 mg/kg of DOM or S(+)AMPH from saline.*

DOM-trained rats. Under these conditions, DOM failed to elicit more than 33 percent AMPH-like responding at doses of up to 2.7 mg/kg (figure 4); higher doses resulted in disruption of behavior. Likewise, 2,4,5-TMA and 3,4,5-TMA failed to produce more than 25 percent AMPH-appropriate responding (figure 5). Doses of 2,4,5-TMA greater than 15 mg/kg produced disruption of behavior. 3,4,5-TMA was evaluated at doses of up to 40 mg/kg; although at the higher doses the animals' response rates were reduced by about 60 percent, responding was essentially saline-like.

Similar results were obtained with 2,5-DMA (figure 4); doses of up to 40 mg/kg failed to engender more than 45 percent AMPH-appropriate responding. N-Monomethylation of AMPH-like agents usually enhances their amphetamine-like properties; consequently, the N-monomethyl analog of 3,4,5-TMA was evaluated (figure 5); here too, doses of up to 40 mg/kg resulted

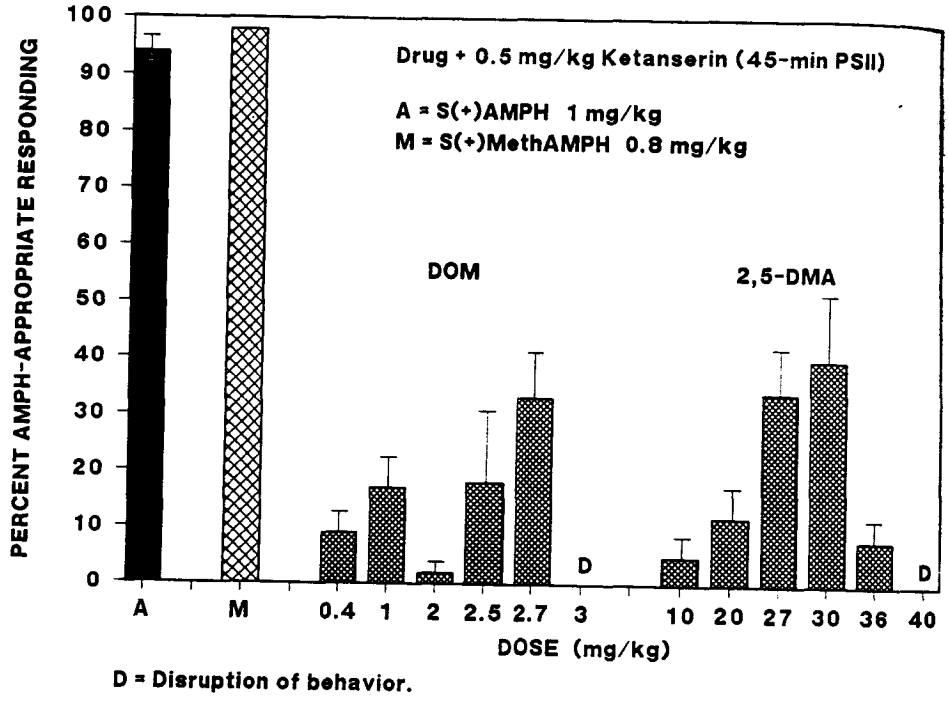
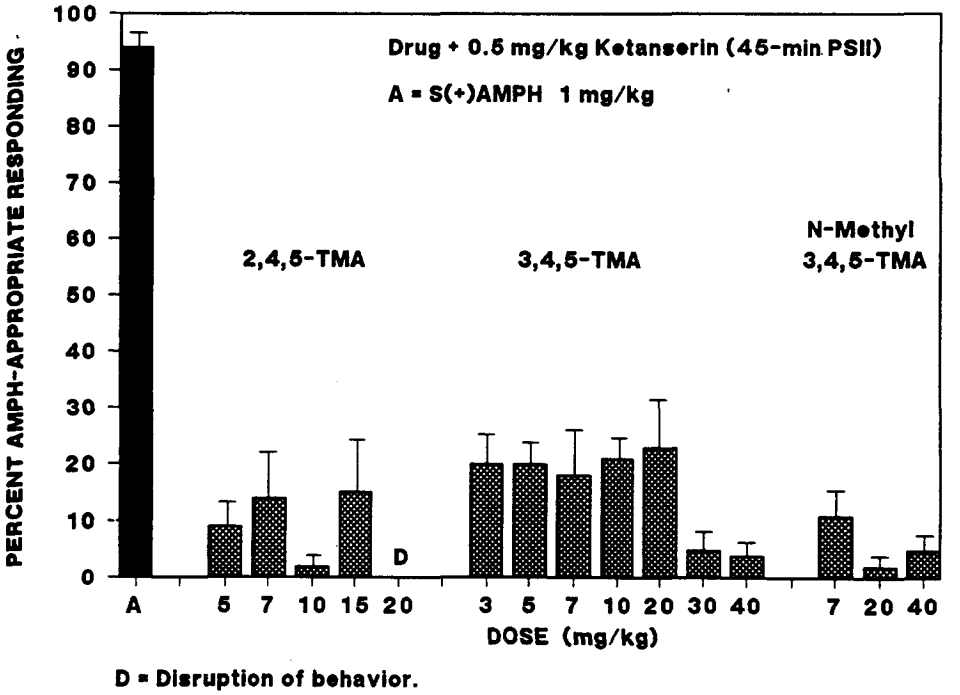


FIGURE 4. *Tests of (+)amphetamine generalization to (+)amphetamine (A), (+)methamphetamine (M), DOM, and 2,5-DMA in rats pretreated with 0.5 mg/kg of the 5-HT_2 antagonist ketanserin.*

in AMPH-appropriate responding that did not exceed 11 percent. Although ketanserin binds at D2 DA receptors and may behave as a DA antagonist at high doses, the dose of ketanserin used in the present study had no effect on the AMPH stimulus; that is, 0.5 mg/kg of ketanserin did not attenuate the effect of S(+)AMPH in AMPH-trained animals, nor did this dose of ketanserin interfere with AMPH-stimulus generalization to 0.8 mg/kg of S(+)methAMPH (figure 4). The results suggest that these agents do not produce AMPH-like stimulus effects at the doses evaluated and further support lack of significant dopaminergic involvement in their mechanism of action.

Pharmacokinetic Investigations

The DD paradigm can be used to investigate the pharmacokinetic and biodispositional properties of hallucinogenic agents. Unfortunately, relatively little has been reported in this regard.



D = Disruption of behavior.

FIGURE 5. *Tests of (+)amphetamine stimulus generalization to 2,4,5-TMA, 3,4,5-TMA, and N-methyl 3,4,5-TMA in rats pretreated with 0.5 mg/kg of ketanserin. Rats were trained to discriminate 1 mg/kg of (+)amphetamine from saline.*

Locus of Action. The specific locus of action mediating the stimulus effects of hallucinogenic agents is unknown. However, it seems likely that hallucinogens produce their stimulus effects via a central mechanism. Several lines of reasoning support this notion. For example, xylamidine (a 5-HT_2 antagonist that does not readily penetrate the blood-brain barrier) is ineffective in attenuating the stimulus effects of the classical hallucinogens. Also, although 5-OH DMT and 5-OMe DMT share similar 5-HT_1/5-HT_2 binding profiles, the 5-OMe DMT stimulus only partially generalizes to 5-OH DMT; the latter agent is of low lipophilicity and is known to poorly penetrate the blood-brain barrier. Another agent that should not penetrate the blood-brain barrier is the quaternary analog of DOB (i.e., QDOB). In animals trained to discriminate R(–)DOB from saline, stimulus generalization does not occur with QDOB. However, it has been demonstrated that QDOB does not bind at 5-HT_2 sites. Minnema et al. (1980) conducted DD studies in which animals were implanted

with indwelling cannula; in this manner, hallucinogens could be administered directly into the brain. Although this technique has not been widely used to investigate such agents, it could prove valuable for investigating (1) agents that do not readily penetrate the blood-brain barrier and (2) specific locations in the brain that might be responsible for mediating the stimulus effects of hallucinogens.

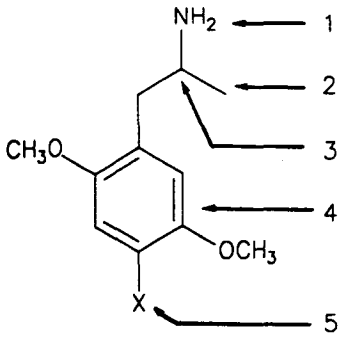
Temporal Properties. The time of onset and the duration of action of the stimulus effects of various hallucinogenic agents have been examined. Of course, these vary from agent to agent; the interested reader is referred to the primary literature for details of such investigations.

Action of Metabolites. Although relatively little work has been done, there is no evidence that the stimulus effects of classical hallucinogens are due primarily to their metabolites. Phenylisopropylamines undergo parahydroxylation in vivo, and it has been speculated that 4-OH 2,5-DMA might be a metabolite of 2,5-DMA. The 4-COOH derivative of 2,5-DMA is a metabolite of DOM. Neither of these agents produces DOM-like stimulus effects in rats, nor do they bind at 5-HT_2 receptors. Iodinated compounds can undergo a rapid deiodination in vivo; thus, the possibility exists that DOI, the iodo counterpart of DOM, may be metabolized to 2,5-DMA. In DD studies, DOI is significantly more potent than 2,5-DMA and the potencies of both compounds are consistent with their affinities for 5-HT_2 receptors. It appears unlikely that the stimulus effects of DOI are due to its deiodinated derivative 2,5-DMA. DD may be a useful procedure for examining the activity of metabolites or potential metabolites, particularly if this approach is coupled with cannulation studies (as mentioned above) in order to avoid potential problems associated with penetration of the blood-brain barrier.

Structure-Activity Relationship (SAR)

That the SAR of LSD has been neglected is probably a direct consequence of the unavailability of LSD analogs. On the other hand, extensive SAR studies have been conducted with 5-OMe DMT and DOM as training drugs; indeed, the SAR of no other training drug has been as widely investigated as that of DOM. The 2,5-dimethoxy substitution pattern of DOM is important. In general, little can be done to increase the potency of DOM-like agents; the only structural modifications that result in more potent DOM-like agents are replacement of the 4-methyl group of DOM with an ethyl (DOET) or n-propyl (DOPR) group, or with certain halogens such as bromo (DOB) and iodo (DOI). The R(–)isomers of

DOM-like agents are several times more potent than their S(+)enantiomers, whereas the reverse is true for derivatives of α-methyltryptamine. In neither series does stereochemistry play a major role. The SARs of these agents have been reviewed in detail (Glennon 1989*a*) and are summarized in figure 6. Readdressing the structural similarity between the DOM-like agents and the phenylisopropylamine stimulant AMPH, a separate and distinct SAR has been formulated for AMPH-like stimulus effects; these are summarized in figure 7.



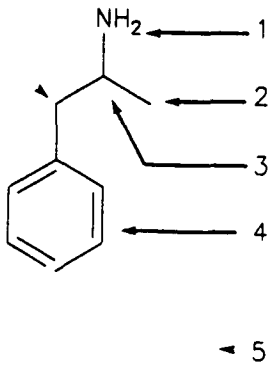
STRUCTURE - ACTVITY RELATIONSHIPS (SAR)

1. Terminal amine:
   - Primary amine optimal
   - Alkyl substituents decrease potency
2. α-Methyl group:
   - Removal decreases potency by 10-fold
   - Homologation reduces potency
3. Chiral center:
   - R-isomers 5 (3-10) times more potent than S
4. Aromatic substituents:
   - Mono-methoxy derivatives are inactive
   - Of the six possible dimethoxy analogs, only the 2,4- and 2,5-DMAs are active
   - All of the six possible tri-methoxy analogs (TMAs) are active
5. Para Substituents:
   - Methyl significantly more potent than H (e.g. DOM > > 2,5-DMA)
   - Other alkyl analogs (Et, nPr) more potent (e.g. DOET, DOPR > DOM)
   - Certain halogen analogs (Br, I) most potent (e.g. DOB, DOI > DOM)
   - Polar substituents (e.g. OH, COOH) inactive

FIGURE 6. *Summary of selected structure-activity relationships important for DOM-like stimulus effects.*

Relationship With Human Hallucinogenic Activity

When DOM-trained animals are used, there is a significant correlation between the stimulus generalization potencies of various classical hallucinogens and their human hallucinogenic potencies. In fact, this was the first example of a correlation between discrimination-derived data and any human measure of activity. Because of the relationship between generalization potency and 5-HT_2



STRUCTURE - ACTIVITY RELATIONSHIPS
FOR AMPHETAMINE - LIKE ACTIVITY

1. Terminal amine:
   - Secondary amine (N-Me) optimal
     (e.g. methamphetamine)
   - Substituents larger than Me less potent
     (Me > H > Et)
2. α-Methyl group:
   - Seems optimal
   - Removal reduces potency
3. Chiral center:
   - S-isomers more potent than R isomers
4. Aromatic substituents:
   - Decrease potency
   - Mono-methoxy analogs weakly active
     (MMA > OMA > PMA > AMPH)
   - Di-methoxy analogs (DMAs) inactive
   - Tri-methoxy analogs (TMAs) inactive
5. Benzylic substituents:
   - Hydroxy groups reduce potency
   - Carbonyl group has no effect
     (e.g. cathinone)

FIGURE 7. *Summary of selected structure-activity relationships important for AMPH-like stimulus effects.*

receptor affinity, there should also be a correlation between receptor affinity and human hallucinogenic potency; such a correlation has been reported (Glennon et al. 1984). Initially, the correlation was demonstrated using rat cortex as the source of 5-HT_2 receptors; this study has now been replicated using human cortex as the source of tissue for the binding studies (Sadzot et al. 1989). Thus, DD studies were directly responsible for aiding our understanding of the mechanism of action of human hallucinogenic activity of the classical hallucinogens.

Role In Drug Development

At first, one might think that DD studies using animals trained to discriminate a classical hallucinogen from saline serve only the investigation of other hallucinogenic agents. This is not the case; hallucinogen-trained animals can be employed in several different applications.

Investigation of Basic Neurochemical Mechanisms. DOM-related agents are fairly selective 5-HT_2 agonists. Indeed, it was speculated that these agents were the first examples of 5-HT_2-selective agonists on the basis of DD studies. SAR for DOM stimulus generalization was later found to parallel SARs for the binding of these agents at 5-HT_2 sites. DOB and DOI are commonly used now as 5-HT_2 agonists, and [^{3}H]DOB and [^{125}I]DOI are commercially available for radioligand binding and autoradiographic studies. DD studies using animals trained to discriminate DOM, DOB, or DOI from saline may serve, then, as a functional behavioral model of central 5-HT_2 receptor activation.

Indicator of Abuse Potential. Hallucinogen-trained animals can be used by the pharmaceutical industry to evaluate the abuse potential of new therapeutic entities. Stimulus generalization to a new agent suggests that the new agent be further evaluated in other tests to determine whether it has any abuse liability. To date, there are no examples of classical hallucinogens that are not recognized by animals trained to discriminate DOM from saline. As mentioned above, however, DD cannot be considered a model of human hallucinogenic activity.

New Drug Development. There is evidence that 5-HT_2 antagonists possess neuroleptic, antianxiety, and antidepressant properties. Thus, animals trained to discriminate a 5-HT_2 agonist could be useful tools for identifying novel 5-HT_2 antagonists. Indeed, examples of this approach have already appeared in the literature (e.g., Meert 1989; Meert and Awouters 1990).

DESIGNER DRUGS

Hallucinogen-related designer drugs were a topic of several recent symposia, and the discriminative stimulus properties of these agents have been reviewed (Glennon 1989*a*, 1989*b*, 1990; Nichols and Oberlender 1989). Separate and distinct SARs have been formulated for the stimulus properties of phenalkylamine hallucinogens and phenalkylamine stimulants (figures 6 and 7). While in the process of formulating the SAR of phenylisopropylamines, we became interested in 3,4-methylenedioxyamphetamine (3,4-MDA, MDA, "Love Drug"). Because the methylenedioxy group was not in our SAR data base, and because MDA had been popular during the 1960s as a mild hallucinogenic agent with central stimulant properties, we investigated this agent and its isomers in DOM- and S(+)AMPH-trained animals. Consistent with its street reputation, MDA was recognized by both groups of animals. Its R(–)-isomer is primarily responsible for DOM-like effects, whereas its S(+)-isomer is primarily

AMPH-like. Likewise, Nichols et al. (1989) have reported that racemic and R(–)MDA, but not S(+)MDA, result in stimulus generalization in LSD-trained rats. To date, MDA is the only phenalkylamine demonstrated to produce both types of effects. Subsequently, animals were trained to discriminate MDA from saline (table 2); confirming the foregoing observations, the MDA stimulus generalizes both to DOM-like and AMPH-like agents.

TABLE 2. *Drug discrimination studies involving methylenedioxy derivatives of amphetamine as training drug in male rats*

Drug and Study	Route	Schedule	PSII	Dose (mg/kg)
MDA				
Glennon et al. 1982	IP	VI-15	15	1.50
Glennon and Young 1984	IP	VI-15	15	1.50
R(–)MDA				
Appel et al. 1990	IP	FR-10	15	1.50
S(+)MDA				
Appel et al. 1990	IP	FR-10	15	1.50
MDMA				
Glennon et al. 1986	IP	VI-15	15	1.00
Schechter 1987	IP	FR-10	20	1.50
Oberlender and Nichols 1988	IP	FR-50	30	1.75
Glennon and Misenheimer 1989	IP	VI-15	15	1.50
MDE				
Boja and Schechter 1987	IP	FR-10	20	2.00
(+)MBDB				
Nichols and Oberlender 1989	—	—	—	1.75

NOTE: PSII = Presession injection interval (min); MDA = 1-(3,4-Methylenedioxyphenyl)-2-aminopropane; MDMA = N-Methyl MDA or N-Methyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane; MDE = N-Ethyl MDA or N-ethyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane; MBDB = N-methyl-1-(3,4-methylenedioxyphenyl-2-aminobutane; VI-15 = variable interval 15-second schedule of reinforcement; FR-10 = fixed ratio (10) schedule of reinforcement.

Using DOM- and S(+)AMPH-trained animals, we examined several other methylenedioxy phenalkylamines including 2,3-MDA, MMDA (2-methoxy-4,5-methylenedioxy amphetamine), and MDMA (the N-monomethyl derivative of MDA). During the early to mid-1980s, MDMA became a rather popular street drug ("Adam," "Ecstasy"); once it became a scheduled (Schedule I) substance, a series of MDMA-related designer drugs appeared on the clandestine market. Two of the more popular agents include the ethyl homolog of MDMA (MDE, "Eve") and the N-hydroxy analog of MDA (N-OH MDA). We had earlier demonstrated that MDMA differs from MDA in that it produces AMPH-like, but not DOM-like, effects. MDA and MDMA also produce AMPH-like stimulus effects in pigeons (Evans and Johanson 1986) and monkeys (Kamien et al. 1986) trained to discriminate S(+)AMPH from saline, and MDMA produces similar effects in rats trained to discriminate the phenylisopropylamine stimulant cathinone from saline (Schechter 1987). Stimulus generalization occurs between AMPH and cocaine regardless of which is used as training drug, and Broadbent et al. (1989) showed that MDA and MDMA produce cocaine-like effects (though not necessarily complete stimulus generalization, depending on the training dose of cocaine) in rats trained to discriminate cocaine from saline. The S(+)MDA stimulus generalizes to cocaine but only partially generalizes to (+)AMPH (Appel et al. 1990). Oberlender and Nichols (1988) failed to observe AMPH stimulus generalization to MDMA or to either of its isomers; on the basis that the number of animals selecting the drug-appropriate lever never exceeded 25 percent, it was claimed that MDMA lacks AMPH-like character. However, they showed that the MDMA stimulus generalizes to S(+)AMPH, and we have shown that the MDMA stimulus partially generalizes to S(+)AMPH and S(+)methAMPH (Glennon 1990). Although some of the reported inconsistencies may be attributable to differences in technique, there is ample evidence from discrimination studies and others that MDMA is capable of producing some AMPH-like effects. On the other hand, it has never been claimed that MDMA, AMPH, or cocaine produce identical effects. (For example, see Goudie in this volume for a comparison of the stimulus effects of AMPH and cocaine.) On the contrary, all instances of AMPH-stimulus generalization to MDMA have been accompanied by a significant decrease in animals' response rates. Taken together, these results suggest that, although AMPH and MDMA may share some similarities, there also appear to be some differences in their stimulus effects.

MDE and N-OH MDA reportedly produce effects in humans that are similar to those of MDMA. Neither of these agents produces stimulus generalization in AMPH-trained or in DOM-trained animals. However, both agents produce

MDMA-like effects in MDMA-trained rats (Glennon and Misenheimer 1989). These results support the overall contentions of Oberlender and Nichols (1988) that methylenedioxy derivatives of AMPH may possess properties that are distinct from those considered simply AMPH-like or hallucinogen- (e.g., DOM-)like. In contrast to their conclusions, however, it seems very likely that MDA and MDMA possess some AMPH-like qualities. MDE and N-OH MDA, on the other hand, appear to lack significant AMPH-like and DOM-like character.

Relatively little has been reported regarding the SAR of MDMA analogs. The α-ethyl homolog of MDMA (i.e., MBDB) is another MDMA-like agent that lacks AMPH-like and LSD-like stimulus properties; several conformationally restricted analogs have also been evaluated (for a review see Nichols and Oberlender 1989). Recently, we examined a new agent that has been confiscated from several clandestine laboratories: PMMA. PMMA is a structural relative of MDMA that possesses a 4-methoxy group in place of the 3,4-methylenedioxy bridge. This agent, like MDE and N-OH MDA, fails to produce AMPH-like or DOM-like stimulus effects, but it does produce MDMA-like effects (Glennon 1990). On a molar basis, PMMA (ED_{50} = 0.2 mg/kg) is about 3.5 times more potent than MDMA (ED_{50} = 0.76 mg/kg). Consequently it appears that the methylenedioxy group is not essential for MDMA-like activity and that an entirely new SAR may need to be investigated.

SUMMARY

Animals trained to discriminate classical hallucinogens from saline have been used in the past decade to examine other hallucinogenic agents. Time course (onset, duration of action) and locus of action have been studied, SARs have been formulated, and mechanism of action has been investigated in detail. On the basis of DD studies in animals, it was proposed that hallucinogenic agents may produce their actions in humans via a 5-HT_2 agonist mechanism and that certain phenalkylamine hallucinogens such as DOM and DOB might constitute the first known examples of 5-HT_2 agonists. This led to the development of $^{[3]}$HDOB and [^{125}I]DOI for use in radioligand binding and autoradiographic studies and to the use of hallucinogen-trained animals as a functional behavioral model of 5-HT_2 receptor activation. Animals trained to classical hallucinogens are more recently being used to evaluate novel designer drugs. It can be seen, then, that this paradigm, using hallucinogenic agents as training drugs, has proven to be quite useful for the investigation of hallucinogens and nonhallucinogens alike.

Note added in proof: We have recently found that both the DOM stimulus and the MDMA stimulus can be attenuated by pretreatment of the animals with very small doses of the 5-HT_3 antagonist zacopride. Zacopride (0.001 mg/kg) in combination with the training doses of DOM and MDMA (1 and 1.5 mg/kg, respectively) reduces drug-appropriate responding from >90 percent to <25 percent in both groups of animals. These findings offer entirely new insight into the mechanism of action of hallucinogenic agents and designer drugs as discriminative stimuli; they suggest that 5-HT_3 antagonists are capable of modulating the effects of these agents and that they may be of value for antagonizing the effects of these agents in a clinical setting.

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