



# Arylalkylamine Drugs of Abuse: An Overview of Drug Discrimination Studies

RICHARD A. GLENNON

*Department of Medicinal Chemistry, Virginia Commonwealth University, Richmond, VA 23298-0540*

GLENNON, R. A. *Arylalkylamine drugs of abuse: An overview of drug discrimination studies.* PHARMACOL BIOCHEM BEHAV 64(2) 251–256, 1999.—Abused arylalkylamines fall into two major categories: the indolealkylamines, and the phenylalkylamines: These agents can be further subclassified on the basis of chemical structure. Examples of these agents possess hallucinogenic, stimulant, and other actions. Drug-discrimination techniques have been used to classify and investigate this large family of agents. Such studies have allowed the formulation of structure–activity relationships and investigations of mechanisms of action. Arylalkylamine designer drugs also possess the same or a combination of actions, and are being investigated by the same methods. © 1999 Elsevier Science Inc.

Hallucinogens    Stimulants    Empathogens    DOM    Amphetamine    Designer drugs    MDMA    MDA  
 PMMA    α-ET

SIMPLE arylalkylamines possess the common structural moiety **Ar-C-C-N** where Ar is typically an indole (i.e., the indolealkylamines) or phenyl group (i.e., the phenylalkylamines). The arylalkylamine moiety is also found embedded in a number of other structurally more complex agents (e.g. opiates), but it is the more elaborate nature of these latter structures that accounts for their different pharmacological actions; the complex arylalkylamines will not be discussed herein. Simple arylalkylamines are among a group of agents that has seen widespread abuse. Actions typically associated with these agents include (a) hallucinogenic activity, (b) central stimulant activity, and (c) other activity. This last group encompasses, in particular, the so-called designer drugs that may display hallucinogenic, central stimulant or empathsenic activity, or a combination of activities.

## CATEGORIZATION OF AGENTS

Arylalkylamines (AAAs) can be divided into the indolealkylamines (IAAS) and the phenylalkylamines (PAAs). These can be further subdivided into different subclasses. The indolealkylamines are divided into the N-substituted tryptamines, α-alkyltryptamines, ergolines or lysergamides, and (tentatively) the β-carbolines (Fig. 1). The phenylalkylamines are subdivided into the phenylethylamines and the phenylisopropylamines (Fig. 1). The actions of these agents can be highly dependent upon the nature of various substituent groups (i.e., in Fig. 1, R, R', and R'').

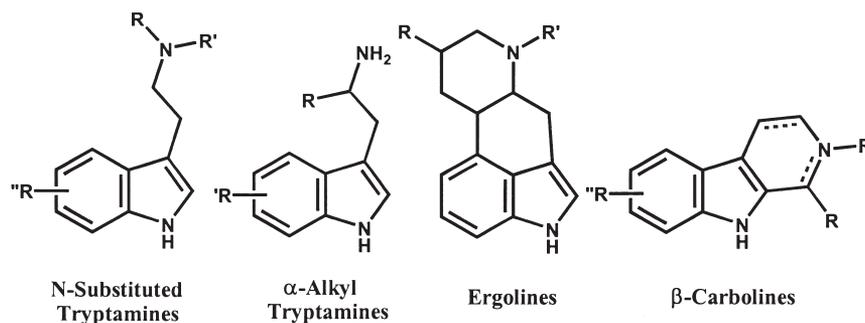
## HALLUCINOGENS

Hollister (12) defined hallucinogens or psychotomimetic agents as those that produce changes in thought, mood, and

perception with little memory or intellectual impairment, and that produce little stupor, narcosis, or excessive stimulation, minimal autonomic side effects, and that are nonaddicting. As restrictive as this classification might appear, Hollister was able to define a number of different classes of agents (Table 1) that have since been shown to be behaviorally dissimilar in humans [see (7) for further discussion]. That is, hallucinogenic agents are a pharmacologically diverse and heterogeneous group of agents. Agents in the Hollister classification scheme include, for example, phencyclidine (PCP), cannabinoids (e.g., tetrahydrocannabinol or THC), and LSD-like agents. There now is evidence that these agents produce dissimilar effects and likely work through distinct mechanisms. We have attempted to subcategorize some of these agents and have identified what we term the “classical hallucinogens.” The classical hallucinogens are agents that meet Hollister’s original definition, but are also agents that: (a) bind to 5-HT<sub>2</sub> serotonin receptors, and (b) are recognized by animals trained to discriminate 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) from vehicle (6). This will be further discussed below.

Some of our early studies were devoted to determining which arylalkylamines produce a common effect. To this extent we employed the drug discrimination paradigm, with animals trained to a suitable training drug, to determine which agents produce stimulus effects similar to those of a known hallucinogen. However, the question immediately arises as to which hallucinogen should be used as the training drug? Obviously, the selection of training drug could influence any subsequent classification scheme. We investigated examples from the different classes of arylalkylamines. For example, we explored the N-substituted tryptamine 5-methoxy-N,N-dimeth-

## INDOLEALKYLAMINES (IAAs)



## PHENYLALKYLAMINES (PAAs)

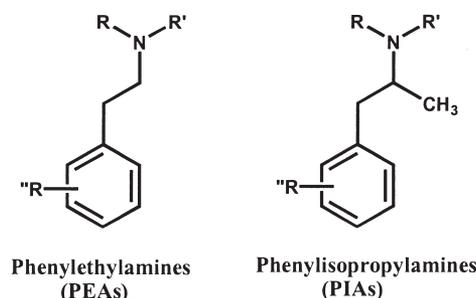


FIG. 1. General structures of the two chemical classes of arylalkylamines: the indolealkylamines and the phenylalkylamines.

yltryptamine (5-OMe DMT), the ergoline lysergic acid diethylamide (LSD), the phenylethylamine mescaline, and the phenylisopropylamines DOM, *R*(-)-DOB or *R*(-)-1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane, and DOI or 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane. Eventually, we settled on the use of DOM-trained animals to continue our studies. The DOM-stimulus generalized to 5-OMe DMT and other examples of N-substituted tryptamines; 5-methoxy- $\alpha$ -methyltryptamine, and other examples of  $\alpha$ -alkyl-tryptamines; the ergoline LSD, the phenylethylamine mescaline, and other examples of phenylethylamines, and to DOB, DOI, and other examples of phenylisopropylamines (5). The DOM-stimulus also generalized to several different examples of  $\beta$ -carbolines such as harmaline (5). As if to underscore the stimulus similarity among these agents, stimulus generalization occurred among DOM, mescaline, LSD, and 5-OMe DMT, regardless of which was used as the training drug. Thus, using DOM-trained animals, it was possible to determine which of several hundred agents produced DOM-like stimulus effects in animals. Figure 2 shows representative dose-response curves for DOM-stimulus generalization to examples of the different classes of arylalkylamines.

At this point it might be noted that no claim is made that these agents all produce identical effects. Indeed, the effects of some of these agents can be distinguished by humans. The claim is made, however, that these agents produce a common DOM-like stimulus effect in rats [reviewed: (5,7)].

Subsequently, it was demonstrated that the stimulus potencies of about two dozen agents were highly correlated with

the reported human hallucinogenic potencies of these same agents. During investigations of the mechanisms underlying the stimulus effects of DOM it was found that certain serotonin (5-HT) antagonists were able to block the stimulus effects of DOM. Later studies demonstrated that 5-HT<sub>2</sub> antagonists, in particular, were especially effective. Thus, the idea was borne that hallucinogens might be producing their stimulus effects via a 5-HT<sub>2</sub> agonist mechanism. If the classical hallucinogens act as direct-acting 5-HT<sub>2</sub> agonists, it might be possible to demonstrate a relationship between their potencies and their 5-HT<sub>2</sub> receptor affinities. Indeed, we found that a signif-

TABLE 1  
HOLLISTER'S CLASSIFICATION OF  
PSYCHOTOMIMETIC AGENTS (12)

| Classes of Psychotomimetic Agents | Examples                                |
|-----------------------------------|---|
| Lysergic acid derivatives         | Lysergic acid diethylamide (LSD)        |
| Phenylethylamines                 | Mescaline                               |
| Indolealkylamines                 | N,N-Dimethyltryptamine (DMT)            |
| Other indolic derivatives         | Harmala alkaloids, Ibogaine             |
| Piperidyl benzilate esters        | JB-329                                  |
| Phenylcyclohexyl compounds        | Phencyclidine (PCP)                     |
| Miscellaneous agents              | Kawain, Dimethylacetamide, Cannabinoids |

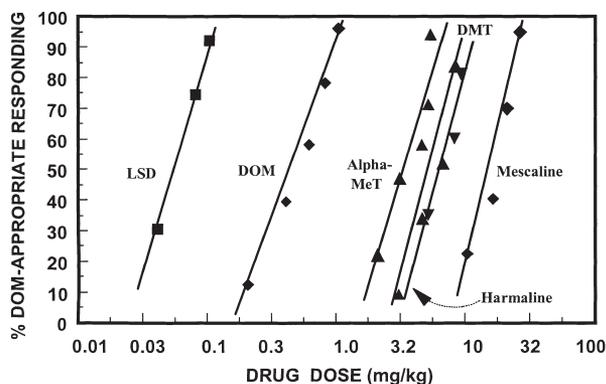


FIG. 2. Dose-response curves showing DOM-stimulus generalization to representative examples of the arylalkylamines: the ergoline lysergic acid diethylamide (LSD), the phenylisopropylamine DOM, the  $\alpha$ -alkyltryptamine  $\alpha$ -methyltryptamine ( $\alpha$ -MeT), the N-substituted tryptamine *N,N*-dimethyltryptamine (DMT), the  $\beta$ -carboline harmaline, and the phenylethylamine mescaline.

icant correlation exists between DOM-derived stimulus generalization potency, human hallucinogenic potency, and 5-HT<sub>2</sub> receptor affinity for a large series of agents (6). The phenylalkylamines have not been shown to bind with high affinity at any population of receptors other than 5-HT<sub>2</sub> serotonin receptors. In contrast, indolealkylamines can be quite nonselective. That is, many tryptamine derivatives bind at multiple populations of 5-HT receptors, and the tryptamine-containing ergoline LSD is particularly promiscuous in this regard. Nevertheless, all the classical hallucinogens share common binding at 5-HT<sub>2</sub> receptors. This was termed the 5-HT<sub>2</sub> hypothesis of hallucinogenic drug action [reviewed in (7)].

Since this hypothesis was first proposed, 5-HT<sub>2</sub> receptors have been found to represent a family of three subpopulations: 5-HT<sub>2A</sub>, 5-HT<sub>2B</sub>, and 5-HT<sub>2C</sub> receptors (also referred to in some of the earlier literature as 5-HT<sub>2</sub>, 5-HT<sub>2F</sub>, and 5-HT<sub>1C</sub> receptors, respectively). The classical hallucinogens bind at all three subpopulations (15). Recent work by Ismaiel et al. (14) Schreiber et al. (17), and Fiorella et al. (3) indicate that the stimulus effects of DOM-derived agents involve a 5-HT<sub>2A</sub> rather than 5-HT<sub>2C</sub> mechanism. Furthermore, agents such as AMI-193 and ketanserin, 5-HT<sub>2</sub> antagonists that display relatively low affinity for 5-HT<sub>2B</sub> receptors, potentially antagonize the DOM stimulus suggesting that it is unlikely that the DOM stimulus is 5-HT<sub>2B</sub>-mediated (15).

As of this time, two properties that the classical hallucinogens have in common is that (a) they bind at 5-HT<sub>2A</sub> receptors and (b) they are recognized by DOM-trained animals. Hence, we have used these criteria to define the classical hallucinogens (7). Using radioligand binding and drug discrimination, the structure-activity relationships of these agents have been investigated; a detailed discussion of structure-activity relationships has been recently reviewed (5).

The  $\beta$ -carbolines represent an interesting group of agents. Examples of  $\beta$ -carbolines, such as harmaline (Fig. 1), are known to be hallucinogenic in humans [see (10) for discussion]. We have demonstrated that DOM-stimulus generalization occurs to harmaline (Fig. 2). Recently, we reported that harmaline binds at 5-HT<sub>2A</sub> (and at 5-HT<sub>2C</sub>) receptors (10). Furthermore, animals have been trained to discriminate harmaline from saline vehicle and administration of DOM resulted in a maximum of 76% harmaline-appropriate respond-

ing, suggesting that similarities exist between the stimulus properties of the two agents. Most recently, however, we have replicated this latter study and have found that administration of DOM to harmaline-trained animals does indeed result in stimulus generalization (i.e., >80% harmaline-appropriate responding) (Glennon and Young, unpublished findings). Because the  $\beta$ -carbolines constitute a very large series of agents that has not been well investigated, it may be premature to decisively include them as members of the classical hallucinogens. However, although additional investigations are obviously required, there seems to be sufficient information to tentatively classify the  $\beta$ -carboline harmaline as a classical hallucinogen.

#### CENTRAL STIMULANTS

The parent unsubstituted phenylisopropylamine is known as amphetamine and amphetamine is a central stimulant. Do other examples of arylalkylamines possess this activity? Actually, this has not been as well investigated as might have been expected. An example of an indolealkylamine, the  $\alpha$ -alkyltryptamine  $\alpha$ -methyltryptamine ( $\alpha$ -MeT) has been demonstrated to behave as a central stimulant in several species of animals (11). Other agents may also possess this action, but their central stimulant actions may be overshadowed by their hallucinogenic nature; this remains to be investigated.

Amphetamine probably represents the prototypical central stimulant, and most related stimulants possess a phenylisopropylamine moiety. Although both optical isomers of amphetamine have been employed as training drugs in drug discrimination studies, (+)amphetamine is without question the more prevalent, and the more potent, of the two [reviewed in (19)]. The phenylisopropylamine central stimulants likely produce their central stimulant and stimulus properties primarily via an indirect dopaminergic mechanism (9, 19). Limited structure-activity relationships have been reported for both activi-

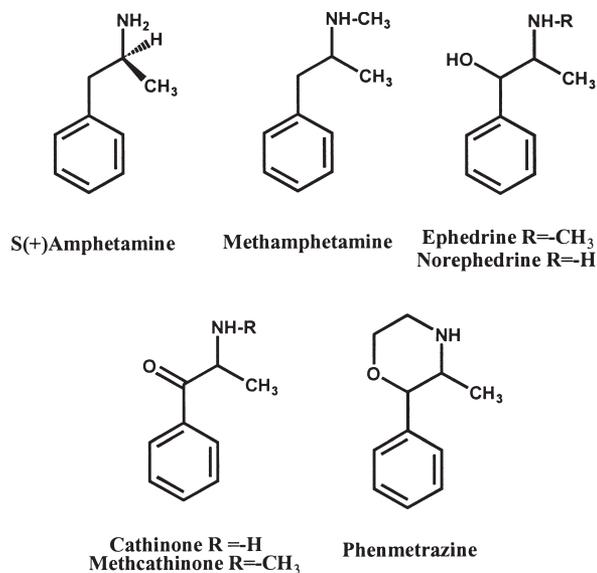


FIG. 3. Chemical structures of S(+)-amphetamine, ( $\pm$ )methamphetamine, and the  $\beta$ -oxidized phenylisopropylamines ephedrine, norephedrine, cathinone, methcathinone, and phenmetrazine. See also Fig. 4 for the stereochemistry associated with ephedrine and norephedrine.

ties (18,19), and there seems to be significant similarities between them.

In general, incorporation of substituents into the aromatic ring dramatically reduces amphetaminergic potency or, as is more often the case, abolishes amphetamine-like stimulus action (19). The nonaromatic portions of the molecule can be modified, however, with interesting consequences. Although N-alkylation of amphetamine results in a progressive decrease in amphetaminergic character as the size of the alkyl substituent is increased, N-monomethylation provides a curious exception; N-monomethylamphetamine or methamphetamine is at least as potent as amphetamine in (+)amphetamine-trained animals and, as with amphetamine itself, the *S*(+)-isomer is several times more potent than the *R*(-)-isomer (see Fig. 3 for chemical structures) (19). Homologation of the  $\alpha$ -methyl group essentially abolishes amphetamine-like stimulus properties whereas removal of this group (i.e., replacement by hydrogen to afford phenylethylamine) decreases potency; the latter effect is probably due to a decrease in lipophilicity and a resulting decrease in the ability to penetrate the blood-brain barrier, as well as to a greater susceptibility to metabolism.

A remaining position that has not yet been mentioned is the benzylic or  $\beta$ -position. Substitution at the  $\beta$ -position has not yet been thoroughly investigated; however, several  $\beta$ -substituted compounds retain amphetamine-like activity. Most of what is known about the  $\beta$ -position relates to  $\beta$ -oxidized analogs of amphetamine (Fig. 3). Incorporation of a benzylic hydroxyl group results in a series of phenylpropanolamines (Fig. 4). The best investigated of these is ephedrine. In (+)amphetamine-trained animals, racemic ephedrine has been reported to result in stimulus generalization (13) or partial generalization (4). Recently, it has been demonstrated that (-)ephedrine, but not (+)ephedrine, elicits (+)amphetamine-like responding in rats (23). Norephedrine has been reported to result in generalization [e.g., (1)] ( $\pm$ )Ephedrine, (-)ephedrine, and norephedrine have been used as training drugs [see (21,23) for discussion]. None of these agents is as potent as (+)amphetamine in drug discrimination studies, and most of the other phenylpropanolamines shown in Fig. 4 have not been examined. One reason why these substances are currently attracting some attention is due to their occurrence in so-called "herbal dietary supplements" such as Herbal Ecstasy<sup>®</sup> and Herbal XTC<sup>®</sup>. These herbal preparations are reportedly prepared using natural ephedra, and ephedra is known to contain a number of phenylpropanolamines, with (-)ephedrine being a major constituent. Oxidation of norephedrine and ephedrine result in cathinone and methcathinone, respectively. Cathinone is a naturally occurring substance found in the shrub *Catha edulis* (khat). Cathinone is at least as potent as amphetamine in drug discrimination studies, and cathinone has been used as a training drug in animals [reviewed in (9)]. Methcathinone is to cathinone what methamphetamine is to amphetamine; that is, methcathinone, known on the street as "CAT," is a potent central stimulant, and is more potent than amphetamine in drug discrimination studies (22)]. *S*(+)Methcathinone recently has been used as a training drug in rats (22). The results of these investigations indicate that  $\beta$ -oxidized derivatives of amphetamine can retain amphetamine-like properties, and that some are actually more potent than amphetamine itself. The hydroxylated analogs likely suffer from problems of reduced lipophilicity and/or metabolism, and are less potent than amphetamine. The carbonylated analogs cathinone and methcathinone, in contrast, are quite potent. Other  $\beta$ -oxidized analogs that retain amphetaminergic activ-

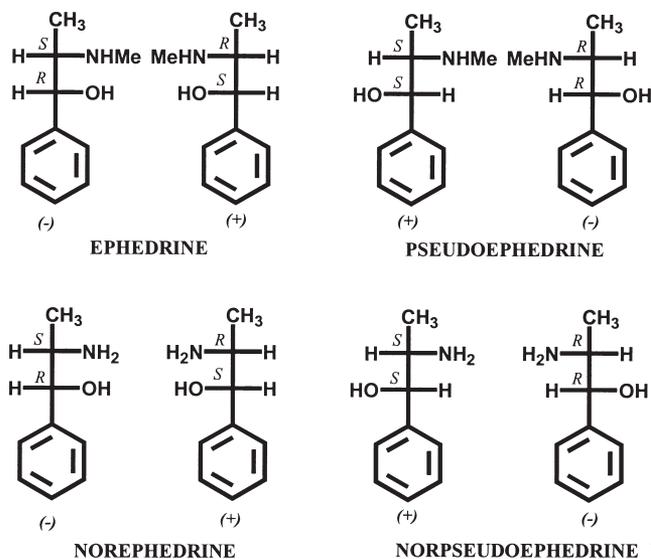


FIG. 4. The phenylpropanolamines. The top row shows the structures and names of the four optical isomers of N-monomethyl phenylpropanolamine, and the bottom row shows the corresponding *N*-desmethyl analogs. (+)Norpseudoephedrine is also known as (+)nor- $\Psi$ -ephedrine or (+)cathine.

ity include cyclic analogs such as phenmetrazine (Fig 3) (19), indicating that the carbonyl group found in cathinone and methcathinone is not per se, a requirement for amphetamine-like stimulus action. Recent results further suggest that the structure-activity relationships of amphetamine analogs and cathinone analogs are not necessarily identical (2).

Although amphetamine probably represents one of the most widely used training drugs in drug discrimination studies (19), there is considerable work that remains to be done on amphetamine analogs and related agents.

#### DESIGNER DRUGS

Designer drugs or controlled substance analogs are structurally modified derivatives of known drugs of abuse. In some instances, it is possible to predict the actions, and sometimes even the potencies, of designer drugs on the basis of established structure-activity relationships. For example, *Nexus* is a designer drug that has made an appearance in the southeastern United States. *Nexus* is 2-(4-bromo-2,5-dimethoxyphenyl)-1-aminoethane or  $\alpha$ -desmethyl DOB (see Fig. 5 for structure of DOB). That is, *Nexus* is the phenylethylamine counterpart of the phenylisopropylamine hallucinogen DOB. Because  $\alpha$ -demethylation of phenylisopropylamine hallucinogens is known to usually result in retention of activity but in a severalfold reduction in potency, it would be expected that *Nexus* would be a DOM-like agent with a potency less than that of DOB. As shown in Fig. 6, this was found to be the case. Thus, certain designer drugs may represent analogs of hallucinogens, whereas other may represent analogs of amphetamine.

However, the actions of designer drugs are not always predictable. A prototypical example is MDMA ("Ecstasy", "XTC", "Adam"). MDMA is the N-monomethyl derivative of MDA or 1-(3,4-methylenedioxyphenyl)-2-aminopropane (Fig. 5). MDA possesses both hallucinogenic and central stimulant actions; the *R*(-)-isomer seems primarily responsible for the former action, whereas the *S*(+)-isomer seems prima-

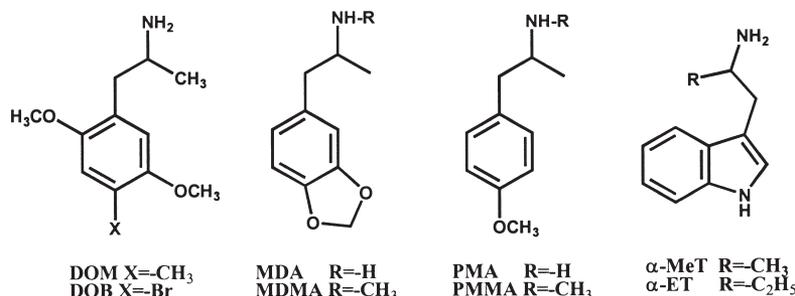


FIG. 5. Chemical structure DOM, DOB, MDA, MDMA, PMA, PMMA,  $\alpha$ -MeT, and  $\alpha$ -ET.

rily responsible for the latter. On the basis of established structure–activity relationships indicating that N-monomethylation decreases (or abolishes) hallucinogenic activity, and that this same structural modification enhances amphetamine-like actions, it might have been expected that MDMA would lack significant hallucinogenic activity but retain central stimulant activity. The results of drug discrimination studies are consistent with this prediction; that is, MDMA produces (+)amphetamine-like, but lacks DOM-like, stimulus effects, regardless of which of the three agents is used as the training drug (5). However, Nichols and co-workers [reviewed in (16)] have argued that MDMA produces, in addition to its stimulant actions, an effect that is uniquely distinct from that of hallucinogens and central stimulants. In humans, MDMA reportedly produces an empathogenic effect (increased sociability, heightened empathy) and has seen some application as an adjunct to psychotherapy. The  $\alpha$ -ethyl homolog of MDMA, MBDB, retains the latter action but lacks amphetaminergic character (16).

Another agent with unpredicted action is *para*-methoxymethamphetamine or PMMA (Fig. 5). PMMA is a structural hybrid of two phenylisopropylamine stimulants: methamphetamine and a weaker stimulant *para*-methoxyamphetamine (PMA). Surprisingly, PMMA lacks central stimulant actions [e.g., fails to result in (+)amphetamine-stimulus generalization, does not produce locomotor stimulation in mice]. PMMA also fails to produce DOM-like effects in DOM-trained animals. However, an MDMA stimulus generalized to

PMMA and PMMA was three times more potent than MDMA. In animals trained to discriminate PMMA from vehicle, the PMMA stimulus failed to generalize to either (+)amphetamine or DOM; the PMMA stimulus, however, generalized to MDMA, and again, PMMA was three times more potent than MDMA (8). It would seem that MDMA and PMMA may share a common stimulus component of action, but that PMMA lacks the amphetamine-like stimulant character of MDMA.

On the basis of the above and other investigations, we have proposed that the phenylalkylamines produce at least three types of stimulus effects in animals: hallucinogenic (H), stimulant (S), and “other” (O) actions (8). These relationships are shown in schematic fashion in Fig. 7. For the time being, and for the purpose of characterization, we consider DOM as the prototypic phenylalkylamine hallucinogen, (+)amphetamine as the prototypical stimulant, and PMMA as a prototypical “other” agent. MDMA can be considered an S/O-type (see Fig. 7) agent in that it produces both effects. In addition to its DOM-like and (+)amphetamine-like effects, MDA produces MDMA-like effects; that is, an MDMA-stimulus generalizes to both optical isomers of MDA. Thus, *R*(–)MDA may be considered an H/O-type agent, *S*(+)MDA and *S*/O-type agent, and ( $\pm$ )MDA an S/H/O-type agent. Other agents have been and are continuing to be characterized as to which of these three types of stimulus actions they produce.

Thus far, we have focussed on the phenylalkylamines. Indolealkylamines, however, might also be classifiable in a similar

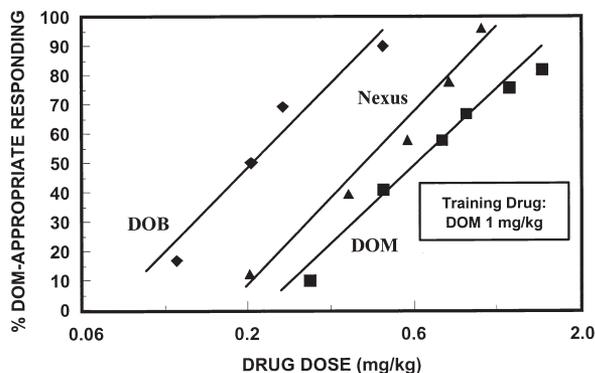


FIG. 6. DOM-stimulus generalization to the phenylisopropylamine hallucinogen 1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane (DOB) and the phenylethylamine designer drug *Nexus* [2-(4-bromo-2,5-dimethoxyphenyl)-1-aminoethane].

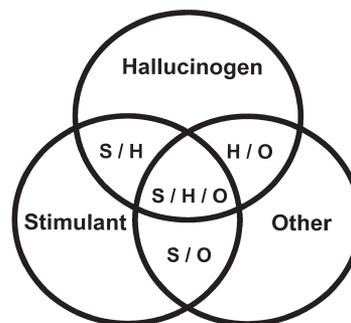


FIG. 7. Proposed relationships between the stimulus effects produced by arylalkylamines. Arylalkylamines can produce effects that can be classified as hallucinogen-like (H), stimulant-like (S), or other (O); see text for further explanation. The classification scheme is adopted from Glennon et al. (8).

fashion. That is, these three types of actions are not necessarily confined to phenylalkylamines. For example,  $\alpha$ -ethyltryptamine ( $\alpha$ -ET), a homolog of  $\alpha$ -methyltryptamine (Fig. 5), is capable of producing multiple effects. A DOM stimulus generalizes to  $S(-)\alpha$ -ET but not to  $R(+)\alpha$ -ET, a (+)amphetamine stimulus generalizes to  $R(+)\alpha$ -ET but not to  $S(-)\alpha$ -ET, and a PMMA or MDMA stimulus generalizes to both optical isomers of  $\alpha$ -ET. It has been suggested that  $\alpha$ -ET might be an indolealkylamine counterpart of MDA (20).

#### SUMMARY

The arylalkylamines can be divided into several chemical categories and into several behavioral categories. The breadth of information available on these agents makes it difficult to offer a comprehensive review in the space provided. And yet, there remain many gaps in our knowledge of these agents. Some structure-activity relationships have been formulated for the different actions, or for certain structure

types, but here, too, more remains to be done. A classification scheme has been proposed to account for the stimulus effects produced by the arylalkylamines; although these relationships have been investigated to some degree for the phenylalkylamines, they have only recently been extended to include the indolealkylamines. The classification scheme shown in Fig. 7 may be overly simplistic, but it provides a new comprehensive and unifying framework with which to view the arylalkylamines. It suggests that there are multiple mechanisms of action and multiple structure-activity relationships. It also provides an explanation for why so many arylalkylamines result in partial generalization, in drug discrimination studies, depending upon the particular agent being used as the training drug.

#### ACKNOWLEDGEMENTS

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