7. STRUCTURE-ACTIVITY RELATIONSHIPS OF MDMA AND RELATED COMPOUNDS: A NEW CLASS OF PSYCHOACTIVE AGENTS?

DAVID E. NICHOLS AND ROBERT OBERLENDER

1. INTRODUCTION

It has been hypothesized that MDMA and substances that possess a psychopharmacological effect similar to MDMA are members of a novel pharmacological class named entactogens [1–3]. In this chapter evidence will be presented to support this, through a discussion of the data acquired in efforts directed toward testing this hypothesis. Although these studies are far from complete, the results gathered thus far, together with those from other laboratories, support the view that the pharmacology of entactogens is clearly different from other known classes of compounds.

1.1. Entactogens, hallucinogens, and stimulants

By definition, the identification of a new drug class results from pharmacological studies that clearly show that its members cannot be included within other known categories. The two drug classes most often mentioned as similar to MDMA are the hallucinogens and central stimulants. As medicinal chemists, our approach to this work has focused on the molecular features (i.e., structure-activity relationships) of the latter in comparison to MDMA-like compounds. The approach employed utilizes the synthesis of a series of structurally related congeners of MDMA and the measurement of their biological activity in terms of MDMA-like, hallucinogen-like, and stimulant-like effects in animal models.

If the hypothesis of novel activity is correct, specific structural modifications

of prototypic molecules should have differing consequences for the three types of activities. These differences would be envisioned to arise from the lack of overlap between the mechanisms by which members of these psychopharmacological classes produce their distinct effects. If the hypothesis is incorrect, molecular modifications in the entactogen class would produce parallel functional changes in one of the other drug classes, indicating that MDMA-like compounds are actually included in one of the known categories.

The chemical structures of representative compounds are illustrated in Figure 1. These are all derivatives of β-phenethylamine. The stimulant amphetamine (1) is simply α-methyl phenethylamine while DOM (2) illustrates the type of aromatic substitution typical for the most potent hallucinogenic phenethylamine derivatives. MDA (3) and MDMA (4) possess a 1,3-dioxole ring fused to the aromatic nucleus.

1.2. Defining activity — therapeutic versus pharmacologic

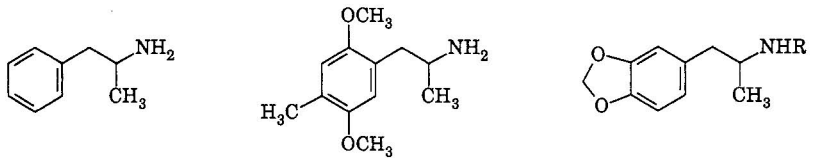
With respect to drugs that have centrally-mediated psychopharmacological effects in humans, the biological action can be defined in two ways. Definitions are commonly derived from the therapeutic goals toward which an activity is applied in the treatment of medical disease states or symptoms. Thus some examples of familiar drug classes include antipsychotics, antidepressants, anxiolytics, and analgesics.

Alternatively, activity may relate to the primary pharmacological effect produced by a drug. Amphetamine and cocaine, for example, are categorized together as stimulants, although the former has been prescribed, among other things, as an appetite suppressant, whereas the latter is useful as a local anesthetic.

For a substance like MDMA, with no currently accepted medical use, primary pharmacological effects must be used to define activity. Since the effects of psychopharmacological agents may be manifested, for example, as changes in mood, perception, and thought, the key question is whether or not humans can distinguish MDMA from other classes of drugs, based on the way it makes them "feel." In other words, does the psychopharmacology of MDMA-like drugs differ in a significant way from that of other drug classes?

Such a determination would ideally be approached by conducting a series of double-blind clinical trails, comparing MDMA with a variety of known substances, such as LSD, mescaline, amphetamine, and cocaine. A range of doses for each agent would be employed. In order to minimize the effects of individual variation, a large number of subjects would be studied. It is probably safe to say that such a detailed comparison will never be made. Nevertheless, there are numerous anecdotal reports that suggest that MDMA is, in fact, different from other known classes of drugs. These are, unfortunately, the best data available at the present time.

The qualitative activity of hallucinogens is generally recognized to vary from subtle at low doses to profound with progressively higher doses. The



AMPHETAMINE (1) DOM (2) MDA (3) R = H

MDMA (4) R = CH_3

Figure 1.

distinguishing feature of these drugs, according to at least one widely used pharmacology text [4], "is their capacity to realiably induce or compel states of altered perception, thought, and feeling that are not (or cannot be) experienced otherwise except in dreams or at times of religious exaltation." Stimulant effects are characterized [5] by wakefulness, alertness, elevation of mood (often with elation and euphoria), a decreased sense of fatigue, increased initiative, self-confidence, ability to concentrate, and increased motor and speech activity.

In contrast to hallucinogens, the effects of MDMA seem to change in intensity yet remain qualitatively similar over the typical dose range of 75–200 mg. An increase in duration and side effects are noted at larger doses. Sensory disruption and loss of contact with reality have not been commonly reported with MDMA. Rather, the primary effect seems to involve enhanced closeness and communication with others, accompanied by positive changes in feelings and attitudes [6]. Like stimulants, MDMA also seems to produce increased talkativeness and mood elevation, but this is apparently not accompanied by increases in initiative, motor activity, or ability to concentrate.

1.3. Determining activity — biochemical and behavioral pharmacology

The type of information gained from anecdotal reports may be valuable in comparing subjective drug effects, yet it lacks the rigor and precision needed for reliable scientific conclusions. For that reason, behavioral and biochemical pharmacological activities have been assayed in a variety of animal models. The results of these investigations have also generally supported the hypothesis that MDMA-like activity is distinct from other known drug classes.

The following discussion of behavioral pharmacology will primarily involve results from drug discrimination (DD) experiments in rats. In this paradigm, drug "states" produced by relatively low doses can be studied in a qualitative and quantitative manner in terms of discriminative stimulus properties. The characteristic subjective effects of a specific training drug at a specific dose, time, and route of administration serve as an interoceptive cue. In the typical procedure, the presence or absence of this cue allows the subject

to choose one of two possible operant responses, in this case pressing a lever in order to obtain a reward. Animals thus learn to discriminate a drug versus non-drug state through training with differential reinforcement; responses on the correct lever are rewarded, whereas responses on the incorrect lever are not.

After the animals acquire the discrimination, substitution tests with new substances are performed. Testing several animals (larger numbers give more reliable results) at several doses, a test drug can be evaluated for the degree of substitution for the training drug, based either on the percentage of tested animals selecting the drug-appropriate lever or the percentage of total responses on the drug lever. Complete substitution (80% or greater drug-appropriate responding) reflects a similarity of activity; lack of substitution (less than 60%) reflects a lack of similarity, and partial substitution (60%–79%) may reflect some degree of overlap.

Using substitution tests in the drug discrimination paradigm, an objective evaluation of the subjective effects of drugs is possible. If two compounds produce essentially similar effects (i.e., are members of the same drug class), one will fully substitute for the other at doses that produce relatively little behavioral disruption. If the profiles of action only partially overlap, complete substitution may still be observed, but relatively large doses might be required to provide the shared effects with sufficient intensity [7]. This means of classification [8] is extremely powerful in studies of centrally active drugs.

It should be kept in mind, however, that a number of variables can influence the results, such as the reinforcement schedule, the numbers of animals and doses tested, and the type of reinforcement used. Therefore, as Overton points out [9], the results of substitution tests have no fixed meaning and must be interpreted with reference to the training paradigm employed.

One of the limitations of DD worth noting is that substitution tests can only indicate whether or not a test drug is *similar* to a training drug [9]. In addition, the DD paradigm is not, in strict terms, a completely valid animal model for human activity, since false positives have been observed. However, it does represent an excellent "first guess" approach to behavioral activity, especially in those cases where the two drugs being compared have been "cross-tested" under similar conditions. If the psychopharmacology of MDMA-like compounds is novel, a series of DD experiments using a variety of training drugs can help to elucidate the nature of its pharmacological characteristics relative to known drug categories.

We have carried out extensive drug discrimination studies using rats trained to discriminate saline from LSD, saline from (+)-amphetamine, saline from (±)-MDMA, and saline from (+)-MBDB (see section 4.1). Table 1 summarizes the results of those experiments. In general, the data demonstrate the similarity between the MDMA and (+)-MBDB training cues. Individual experiments will be considered and we will refer back to the data in Table 1 numerous times in the course of the discussion in this chapter.

Table 1. Drug discrimination results of substitution testing in rats: degree of substitution is expressed as complete (ED_{50} value in μmol/kg), partial (PS), none (NS) or not tested (NT) in this laboratory. All injections were given intraperitoneally, 30 minutes prior to the session.

Test drug	Training drug			
	LSD[a]	(+)-AMP[b]	MDMA[c]	(+)-MBDB[d]
LSD	0.025	NS	PS	PS
DOM	0.61	NS	NS	NS
Mescaline	33.0	NT	NT	NS
(+)-AMP	NS	1.68	4.22	NS
Cocaine	NT	NT	13.9	PS
MDA	4.52	NS	4.06	2.09
(+)-MDA	NS	NS	1.63	1.43
(−)-MDA	2.94	NS	2.27	3.09
MDMA	NS	NS	3.40	3.35
(+)-MDMA	NS	NS	1.92	1.67
(−)-MDMA	NS	NS	5.03	3.09
MBDB	NS	NS	4.19	2.92
(+)-MBDB	NS	NS	3.67	3.28
(−)-MBDB	NS	NS	6.71	6.51

[a] LSD tartrate training dose = 0.08 mg/kg (0.186 μmol/kg).
[b] (+)-amphetamine sulfate training dose = 1.0 mg/kg (5.43 μmol/kg).
[c] MDMA hydrochloride training dose = 1.75 mg/kg (7.63 μmol/kg).
[d] (+)-MBDB hydrochloride training dose = 1.75 mg/kg (7.19 μmol/kg).

2. STRUCTURE-ACTIVITY RELATIONSHIPS — GENERAL CONSIDERATIONS

One can envision at least three areas for structural modification of MDMA. These are illustrated in Figure 2. First, the nature of the amine substituents can be varied; other N-alkyls can be studied, or the nitrogen could be incorporated into a ring system. A second point for structural modification might be the side chain. the alpha-methyl can be extended, or replaced by α,α-dialkylation or the side chain can be incorporated into a ring system fused to the aromatic nucleus to produce rigid analogues. In the following discussion, examples of these types of structural modification and their effects on activity will be presented.

3. STRUCTURE-ACTIVITY RELATIONSHIPS FOR AMINE SUBSTITUENTS

The "parent" compound MDA (3), although classified as an hallucinogenic amphetamine and available on the illicit market for about 20 years, had gained a reputation as the "love drug" [10]. It had been recognized for many years both by recreational drug users and by clinicians [11] that MDA had unique psychoactive properties that were different from hallucinogens, such as LSD or mescaline.

In animal studies, Shannon [12] concluded, based on the work accumulated at that time (1980), that although MDA had effects like both LSD and amphetamine, its mode of action might be like neither of these, and it therefore might represent a unique class of drugs. Subsequent DD studies have shown that

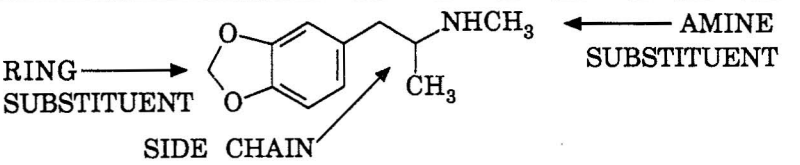


Figure 2.

MDA has stimulus properties similar to hallucinogens [1,13–16], whereas equivocal results have been obtained when the drug was compared with stimulants. Clearly, however, MDA is a psychoactive agent that is not easily categorized.

The results of DD studies in our laboraotry (Table 1) and Shannon's data [12] indicate that MDA does not substitute for (+)-amphetamine. However, complete substitution for (+)-amphetamine was reported by Glennon et al. [16]. One possible explanation for this is that MDA and amphetamine have partially overlapping pharmacological profiles (e.g., on dopaminergic systems). Depending on the paradigm used, shared effects may either be masked by the non-overlapping activity (e.g., on serotonergic systems) or may become apparent at higher doses [7]. The dose of MDA (2.75 mg/kg) required for complete substitution for (+)-amphetamine was, in fact, high and resulted in disruption of two out of the four animals tested [16]. A similar situation was observed for the complete substitution of (+)-amphetamine in MDA-trained rats [16]. This topic is discussed further in section 4.3.

While MDA, especially in high doses, appears to be hallucinogenic or psychotomimetic [17], it seems not to have been used for this action but rather for its effects on mood: production of a sense of decreased anxiety and enhanced self-awareness. Even early reports described the desire of MDA users to be with and to talk to other people [18]. MDA is also the only substituted amphetamine that received serious clinical study as an adjunct to psychotherapy [19, 20].

An important structural feature of MDMA that distinguishes it from hallucinogenic amphetamines is the fact that it is a secondary amine. That is, the basic nitrogen is substituted with an N-methyl, while hallucinogenic amphetamines are most potent as primary amines. In either 3,4,5-substituted or 2,4,5-substituted phenethylamine derivatives, N-methylation decreases hallucinogenic potency by up to an order of magnitude [17].

When MDA is ingested, the hallucinogenic effects last typically 10 to 12 hours, similar to the duration of LSD or mescaline [17]. By contrast, MDMA has a much shorter action, with perhaps a three to five hour duration of effects [21]. There is no evidence that typical doses of MDMA lead to hallucinogenic effects in a significant proportion of users, although in high dosages hallucino-

genic effects have been reported [22]. Thus the simple addition of the N-methyl group limits the temporal course of the action to less than half that of MDA and attenuates or abolishes the hallucinogenic effects that occur with MDA itself.

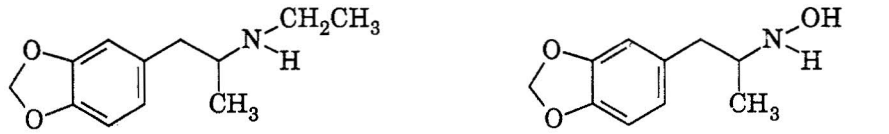
Results from drug discrimination experiments indicate that the cues produced by MDA and MDMA are very similar, since the former completely substitutes for the latter at relatively low doses [3]. Similar results were reported for the substitution of MDMA in MDA-trained rats (1.5 mg/kg) [23] and in fenfluramine-trained rats (2 mg/kg) [24] (see section 5.3). By contrast, relatively high doses, accompanied by significant disruptive effects, were necessary for the complete substitution of (+)-amphetamine in MDMA-trained rats [3].

The drug discrimination results provide evidence for the attenuated hallucinogenic activity of MDMA relative to the primary amine, MDA. Racemic MDMA does not substitute for DOM [14] or LSD [1]. In MDMA-trained rats, DOM does not substitute, whereas LSD at relatively high doses produces partial substitution accompanied by significant behavioral disruption [3].

As with MDA, results from substitution experiments with MDMA in (+)-amphetamine-trained animals are once again equivocal, since complete substitution occurs in some paradigms [23, 25, 26] but not in others [3]. In rhesus monkeys, MDMA was found to be more like amphetamine than MDA, but unlike the training drug, (+)-amphetamine, drug-appropriate responding after both MDMA and MDA was accompanied by large decreases in response rates [26]. These data are discussed in terms of the mechanism of action of MDMA in section 4.3.

A number of investigators have examined the N-ethyl congener of MDMA, MDE (or "MDEA," 5), which seems also to have gained some popularity on the illicit market. In drug discrimination studies, MDE has pharmacological effects that are similar to those of MDMA [27]. Braun et al. [28] have reported that of the N-substituted MDA derivatives that were studied for analgesic action and human psychopharmacology, only the N-methyl (4), N-ethyl (5), and N-hydroxy (6) compounds (Figure 3) were active. The N-hydroxy (6) compound may serve merely as a prodrug for MDA, being metabolically reduced to the primary amine, as has been observed for N-hydroxy-para-chloroamphetamine [29]. It has recently been reported, however, that in drug discrimination experiments, N-OH-MDA, like MDE, failed to substitute for DOM or (+)-amphetamine, while MDA substituted for both in a similar paradigm [30]. The potential metabolic conversion of N-OH-MDA to MDA will have to be studied, especially with respect to time course, before this situation is clarified.

In a recent report by Noggle *et al.* [31], the toxicity of a series of N–alkyl-substituted MDA derivatives was reported and none exceeded the toxicity of MDA itself. Interestingly, these authors point out that the effect of N-methylation on relative toxicity serves as additional evidence that MDA-derivatives



MDE (5) N-OH-MDA (6)

Figure 3.

alter neurotransmission through a mechanism different than amphetamine. That is, N-methylation of amphetamine to yield metamphetamine results in an increase in toxicity, whereas a decrease in toxicity occurs upon N-methylation of MDA to MDMA [32].

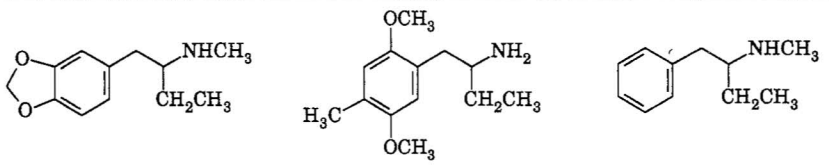
Since the range of modification of N-substitution seems so limited, it appears unlikely that studies of N-substituted MDA analogues will offer additional insight into mechanism of action. However, different N-alkyl groups may affect regional brain distribution and pharmacokinetic properties. For example, the N-ethyl analogue (MDE, 5) has a much shorter biological half-life in rats [27] and humans than does MDMA [17]. N,N-Dialkylation of the nitrogen has been previously reported to abolish the activity of MDA [33].

4. STRUCTURE-ACTIVITY RELATIONSHIPS FOR SIDE CHAIN MODIFICATIONS

4.1. Extension of the α-methyl to an α-ethyl

The most important support for the hypothesis that entactogens represent a unique drug class came from the discovery that the alpha-ethyl homologue of MDMA, MBDB (7), possessed MDMA-like properties in man and in the drug discrimination paradigm in rats [1, 3]. It was known that homologation of the alpha-methyl of the hallucinogenic amphetamines completely abolished hallucinogenic activity [34]. For example, the more active optical isomer of the alpha-ethyl homologue of DOM, BL-3912 (8), was evaluated by a major pharmaceutical firm and found to lack hallucinogenic activity at doses more than 100-fold higher than those effective for DOM [35]. This additional feature of the entactogens, that the alpha-ethyl homologues retained activity, was a most powerful argument that MDMA and certainly MBDB could not fit within the well-established structure-activity relationships of the hallucinogenic amphetamines. The structures of MBDB and BL-3912 are illustrated in Figure 4.

Several studies have characterized MDMA as an amphetamine or cocaine-like agent, based on its stimulus properties or its self-administration in primates [23, 25, 26, 36, 37]. It is well-known that both amphetamine and cocaine have powerful effects on dopamine pathways in the brain, and it seems likely that



MBDB (7) BL3912 (8) (9)

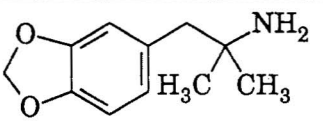
Figure 4.

drugs that release dopamine or stimulate dopamine receptors have reinforcing properties that lead to self-administration and dependence liability [38].

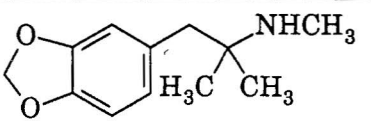
One could not anticipate that the extension of the alpha-methyl of MDMA to an alpha-ethyl would also attenuate the effects of the compound on dopaminergic pathways in the brain. In contrast to MDMA, MBDB has no significant effect either on inhibition of uptake of dopamine into striatal synaptosomes [39] or on release of dopamine from caudate slices [40]. Drug discrimination data support this idea, since amphetamine substitutes for MDMA but not for MBDB. Furthermore, while cocaine fully substitutes in MDMA-trained rats, only partial substitution occurs in (+)-MBDB-trained rats (Table 1). This is further evidence of the decreased effect of MBDB on catecholaminergic systems. These data could be interpreted to suggest that MBDB would not be self-administered in animal models of dependence behavior and, hence, might have low abuse potential. Howver, (+)-MBDB also produces serotonin neurotoxicity in rats, although MBDB is somewhat less toxic than MDMA [Johnson, M.P. and Nichols D.E., unpublished findings].

Based on these data, it seemed likely that an alpha-ethyl moiety might attenuate the ability of other phenethylamines to interact with dopaminergic systems. To test this hypothesis, the alpha-ethyl homolog of methamphetamine (9, Figure 4) was synthesized. This compound (9) was also tested in the drug discrimination paradigm in (+)-amphetamine trained rats and compared with (+)-methamphetamine. The racemic alpha-ethyl homologue was found to possess approximatley one-tenth the potency of (+)-methamphetamine. This supported the speculation that the alpha-ethyl group was generally effective in reducing the impact of phenethylamines on dopaminergic pathways.

Thus for structure-activity studies of MDMA-like substances, emphasis has been placed on the use of (+)-MBDB as the training drug, since it seems to possess a primary psychopharmacology similar to that of MDMA but lacks the "psychostimulant" component of MDMA. That is, MBDB is pharmacologically less complex. Symmetrical transfer of the MDMA and MBDB stimuli indicates that their primary discriminative stimulus effects are very similar. Furthermore, the complete substitution of MDA for both MDMA and (+)-MBDB suggests that the parent compound also possesses similar stimulus properties.



(10a)



(10b)

Figure 5.

4.2. α,α-Dialkylation

Several side chain modified analogues of MDMA and MBDB have now been examined. The earliest studies were of the α,α-dimethyl analogue, 3,4-methylenedioxyphentermine (10a), and its N-methyl derivative (10b), shown in Figure 5. This latter compound proved to lack MDMA-like activity [Shulgin, A.T., unpublished findings]. Interestingly, this compound also lacked the ability to stimulate the release of [^{3}H]-serotonin from prelabeled rat brain synaptosomes [41].

4.3. Stereochemistry and mechanism of action

An important difference between MDMA and the hallucinogenic amphetamines is an observed reversal of stereoselectivity. For every substituted hallucinogenic amphetamine that has been studied, it is the isomer with the *R* absolute configuration in the side chain that is more potent in animal models, in a variety of *in vitro* assays, and in humans. The two isomers differ in potency by a factor of three to ten, depending on the assay system [42]. By contrast, it is the *S* isomer of MDMA that is more potent. This was first reported in experiments with rabbits and in clinical studies [43], and it has recently been confirmed in other animal models [3, 44].

These findings led to the proposal [43], based on the stereoselectivity for the *S*-enantiomer of MDMA, that rather than having a direct effect at serotonin receptors, perhaps MDMA was a neurotransmitter releasing agent acting in a manner similar to amphetamine, where the *S* enantiometer is also more active than the *R*. A subsequent study indicated that the *S* isomers of MDA and MDMA were indeed potent releasers of [^{3}H]-serotonin from prelabeled rat brain synaptosomes [41]. Recently, we reported that MDA and MDMA were also potent releasers of serotonin from superfused hippocampal slices prelabeled with [^{3}H]-serotonin [40]. In all studies to date, whether of release of monoamines from synaptosomes or brain slices or in inhibiting monoamine reuptake into synaptosomes [39], the *S* enantiomer of MDMA is either equipotent to the *R* isomer or is more potent.

It is difficult to trivialize the significance of this argument, since the stereo-

selectivity of biological receptors is accepted as a basic tenet of pharmacology. There is no rationale or experimental precedent for believing that the 3,4-methylenedioxy substitution should do anything that would cause the receptor(s) involved in hallucinogen action to accomodate a side chain stereochemistry reversed from that for phenylisopropylamines with other aromatic substituents.

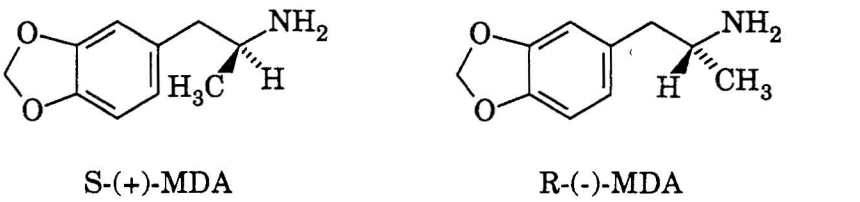
It is clear from the drug discrimination results that the common activity of MDMA and MBDB is not like that of the typical hallucinogenic drugs, LSD, DOM, and mescaline. While LSD seems to be more similar to MDMA than to MBDB, transfer of the training stimulus does not occur to MDMA or MBDB in animals trained to discriminate LSD from saline [1]. Similarly, when DOM was used as a training drug, no substitution was observed for MDMA [14]. In entactogen-trained rats, DOM did not substitute for either MDMA [3] or (+)-MBDB (Table 1).

These results can be interpreted as reflecting the different mechanisms by which entactogens and hallucinogens produce their stimulus effects. Although additional experiments will be necessary to understand the neurochemical events mediating the entactogen cue, they seem to involve presynaptic actions at serotonergic neurons. The evidence for this will be discussed in detail later. By contrast, a variety of experimental data suggests that the stimulus properties of DOM are related to post-synaptic activity at 5-HT_2 receptors [45].

Various experiments have provided evidence for this conclusion. First, selective 5-HT_1 agonists do not substitute for DOM, which, along with several related derivatives, lacks high affinity for 5-HT_1 binding sites. Second, these same compounds have high affinities for 5-HT_2 sites, which are significantly correlated with both ED_{50} values for DOM-stimulus generalization and estimates of human potencies. Third, 5-HT_2 antagonists block the stimulus effects of DOM, as well as DOM-stimulus generalization to mescaline, 5-MeO-DMT, LSD, and quipazine [45]. Similar experiments also implicate a role for 5-HT_2 receptors in the stimulus properties of LSD in rats [46].

However, affinity of MDMA for 5-HT_2 receptors probably cannot be considered significant to its mechanism of action, since the more active *S* isomer has a higher K_I than does the *R* isomer [47]. In pilot experiments, the MDMA or (+)-MBDB cues were not blocked with the selective 5-HT_2 antagonist ketanserin. A similar 5-HT_2 antagonist, pirenpirone, was reportedly ineffective in reversing the disruption of operant responding in mice caused by either isomer of MDMA [48].

Although Callahan and Appel [49] reported that (+)-MDMA and (−)-MDMA substituted for mescaline, (+)-MBDB-trained rats did not recognize the mescaline cue as similar to the training drug (Table 1). Trulson et al. [50] have discussed the involvement of dopaminergic mechanisms in the behavioral effects of mescaline, and it seems possible that its combined activities at serotonin and dopamine neurons may account for a similarity to MDMA and lack of similarity to MBDB.



S-(+)-MDA R-(-)-MDA

Figure 6.

The results of experiments with the isomers of the parent compound MDA (Figure 6) provide an important perspective for a discussion of stereoselectivity. Several studies have now clearly shown that it is the *R* enantiomer of MDA that has the hallucinogenic effects of the racemate, while it is the *S* enantiomer that possesses more potential MDMA-like properties in animal models (1, 3, 14, 17, 41, 43]. Although *S*-(+)-MDA sometimes appears similar to stimulants in the drug discrimination assay in rats [23, 51], it is not generally realized that the effects of (+)-MDA in humans qualitatively resemble those of MDMA rather than amphetamine [Shulgin, A.T., personal communication].

One can view this as a rather unique situation. Both enantiomers of MDA are active but differ in qualitative effect. Thus, if the psychopharmacology of (+)-MDA is like that of MDMA, then N-methylation has little effect on the entactogenic properties of this enantiomer but serves primarily to attenuate the hallucinogenic activity of *R*-(−)-MDA. Drug discrimination data provide evidence for this since (−)-MDA substitutes for hallucinogenic training drugs [1, 13, 14], whereas (−)-MDMA does not [1, 14]. However, (−)-MDA also substitutes for MDMA, and one could envision that the psychopharmacology of racemic MDA might be viewed as comprised of the hallucinogenic and entactogenic properties of the (−)-isomer and the entactogenic and psychostimulant properties of the (+)-isomer. This is a perfect example of why detailed studies of the mechanism of action of psychoactive compounds should be done with the pure optical isomers!

The net effect of (±)-MDA can really be viewed as the result of the simultaneous actions and interactions of two different drugs that happen to be enantiomers. Varying the dose of racemate can alter the psychopharmacological properties in a manner that depends on the potency of each isomer in producing its distinct activity.

Some confusion may currently exist as to which isomer of MDA is more potent, as a consequence of the differing qualitative effects of the enantiomers. In contrast to initial reports [17], there is now evidence that the activity of (+)-MDA is actually greater than that of (−)-MDA. For example, (+)-MDA was found to be the most potent compound tested in substituting for both MDMA and (+)-MBDB, although the (−)-isomer also has entactogen activity (Table

1). Similarly, when racemic MDA (1.5 mg/kg) was used as a training drug [23], (+)-MDA was found to be more potent than (−)-MDA. Thus, entactogens, as studied in rats trained to discriminate MDA [23], MDMA, or (+)-MBDB from saline, consistently demonstrate *stereoselective* action ($S > R$).

Similar stereoselectivity is observed for the stimulant activity of amphetamine and related compounds, such as cathinone [52]. However, the *R* isomers of MDA, MDMA, and MBDB do not substitute for (+)-amphetamine, whereas *S*-(+)-MDA and *S*-(+)-MDMA substitute for (+)-amphetamine in some tests [23, 30] but not in others [3, 51, Table 1]. Thus, the "amphetamine-like" activity of both MDA and MDMA, in cases where it has been observed, is stereo*specific* [53], rather than stereo*selective*.

Ariëns [54] has noted that if a compound has multiple pharmacological actions and if the eudismic ratios (activity of the more active stereoisomer ÷ activity of the less active stereoisomer) differ for the different effects, this indicates that these effects are based on different mechanisms involving different receptors. It seems unlikely, therefore, that MDMA-like and (+)-amphetamine-like activities are identical.

Furthermore, although the N-ethyl derivative of MDA shares stimulus properties with MDMA [27], and N-OH-MDA is reportedly similar in its actions to MDA [28], neither substitutes for (+)-amphetamine under conditions identical to those used when complete substitution of MDA and MDMA for (+)-amphetamine was reported [30]. By contrast, the N-ethyl and N-OH derivatives of amphetamine were observed to completely substitute for (+)-amphetamine [30]. Thus, either an ethyl or a hydroxy substitutent on the nitrogen abolishes the "amphetamine-like" effects of MDA but not amphetamine itself. This difference in structure-activity relationships lends further support to the concept of different mechanisms for entactogen and stimulant activities.

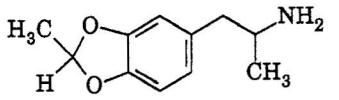
5. AROMATIC SUBSTITUENT-ACTIVITY RELATIONSHIPS

At the present time, little is known about requirements for particular aromatic ring substituents for a compound to possess MDMA-like activity. The largest group of substituted amphetamines with significant hallucinogenic potency possess either 3,4,5- or 2,4,5-trisubstitution patterns [42], whereas stimulant activity is generally attenuated by any aromatic substitution [53].

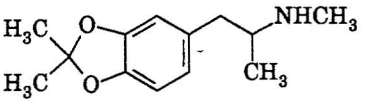
5.1. The 3,4-disubstitution

One of the structural features of MDMA that is somewhat unusual is the fact that it is 3,4-disubstituted. MDA, MDMA, and MBDB all possess the 3,4-methylenedioxy function, and there apparently are no other *active* compounds presently known that fall within the substituted amphetamine class that have substituents only in the 3 and 4 positions.

The isomer of MDA with a 2,3-methylenedioxy substituent has been found to completely substitute for 3,4-MDA, with a potency estimated at 20% of the



(11)



(12)

Figure 7.

latter, but it does not substitute for either DOM or (+)-amphetamine [55]. This example once again illustrates that compounds with entactogen-like activity may differ from both hallucinogens and stimulants.

5.2. Additional methoxy groups

Shulgin [33] has previously summarized the effects on hallucinogenic activity when either one or two methoxy groups are added to 3,4-MDA or 2,3-MDA. Many of these derivatives are potent hallucinogens, but they have not as yet been evaluated for MDMA-like activity. Interestingly, while the addition of an ortho-methoxy to amphetamine results in a compound that retains stimulant activity [53], the same modification to MDMA abolishes its ability to substitute for (+)-amphetamine [56].

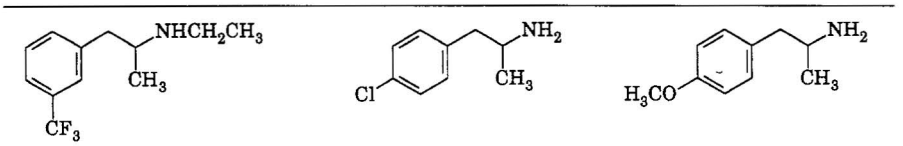
5.3. Alkylation of the dioxole ring

Substitution on the methylene group between the two oxygens of MDMA's benzodioxole ring has been examined. The 3,4-ethylidenedioxy and 3,4-isopropylidenedioxy compounds (11 and 12, Figure 7) were tested for ability to substitute in LSD-trained or MDMA-trained rats in the drug discrimination paradigm. Both compounds gave full substitution in rats trained to either drug. Those results and comparison data for MDA are given in Table 2. Addition of steric bulk to the dioxole ring reduces but does not abolish CNS activity, whether defined as LSD-like or MDMA-like. At the training doses employed, both 11 and 12 were more potent in mimicking MDMA than LSD, based on their ED_{50} values.

Table 2. Results of drug discrimination substitution testing of dioxole-ring-alkylated MDA analogues in rats: ED_{50} values in μmol/kg (95% confidence interval).

Test drug	Training drug[a]	
	LSD	MDMA
MDA (3)	4.52 (3.11–6.57)	4.06 (2.59–6.38)
EDA (11)	13.39 (7.13–25.12)	8.09 (4.28–15.31)
IDA (12)	29.25 (14.75–57.99)	21.41 (12.51–36.66)

[a] Doses, presession time interval, and route of administration same as in Table 1.



FENFLURAMINE (13) PCA (14) PMA (15)

Figure 8.

5.3. Fenfluramine — The meta-trifluoromethyl substituent

Fenfluramine (13) was the product of a search for antiobesity agents with decreased stimulant, toxic, and hypertensive effects relative to amphetamine [57]. Clinical studies with this compound have demonstrated its effectiveness in weight-loss programs and its lack of mood elevating properties [58]. In fact, fenfluramine seems to produce overall effects characterized as unpleasant, sedative, and qualitatively different from those of amphetamine [59, 60] and, apparently, from those of entactogens. Figure 8 shows the structures of fenfluramine and two other pharmacologically similar compounds with para-substituents, para-chloroamphetamine (PCA) and para-methoxyamphetamine (PMA).

In contrast to these differences in human psychopharmacology, the discriminative stimulus properties of racemic fenfluramine have been well studied and, in many respects, appear similar to those of (+)-MBDB. Fenfluramine substitutes for (+)-MBDB at relatively low doses (Table 1), and Schechter [24] has reported that MDMA substituted for fenfluramine. In studies where stimulants have been tested in fenfluramine-trained rats, no substitution occurred for (+)-amphetamine [61–63]. Furthermore, the dopamine antagonist haloperidol, which effectively blocks the discriminative stimulus properties of both (+)-amphetamine and cocaine [64], does not affect the fenfluramine cue [61]. Similarly, haloperidol was found to have no effect when given prior to the training dose of (+)-MBDB (see Table 3).

In exploratory studies, pretreatment of MDMA-trained rats with haloperidol failed to block the MDMA discriminative stimulus. These results may reflect the non-critical nature of the dopamine component in the discriminative stimulus properties of MDMA. It seems likely that the serotonergic component may be more significant to the behavioral effects. Support for this speculation is found in Schechter's work [24], where MDMA was observed to substitute for the serotonergic agent fenfluramine at lower doses and with less disruption than was observed for the substitution of MDMA for the stimulant l-cathinone.

The interpretation of experimental results involving racemic fenfluramine is complicated by the pharmacological differences between the enantiomers [65], the activity of the N-dealkylated metabolite, norfenfluramine [62, 63, 66],

Table 3. Results of attempts to block the cue produced by the training dose of (+)-MBDB (1.75 mg/kg) in drug discrimination testing.

Drug	Action	Dose (mg/kg)	Time[a]	N	Result[b]
Fluoxetine	Serotonin	2.5	90	4	100%
	Uptake	5	90	6	83%
	Inhibitor	10	90	4	100%
Metergoline	Serotonin	0.125	90	5	80%
	Antagonist	0.25	90	6	50%
		0.5	90	7	29%
Haloperidol	Dopamine	0.05	45	5	100%
	Antagonist	0.1	45	5	100%
		0.25	45	6	83%
		0.5	45	5	D[c]

[a] Presession time interval in minutes; (+)-MBDB given at the usual time of 30 minutes.
[b] Results are expressed as the percentage of rats selecting the drug lever.
[c] D = ⅘ rats were disrupted or failed to finish 50 presses on one lever in five minutes. One rat responded on the (+)-MBDB appropriate lever.

and the temporal variation in effects [67]. It does seem likely, though, that the similarity between fenfluramine and entactogens may relate to common neuronal actions. The more potent *S*-(+)-isomer of fenfluramine seems to produce its effects through a release of serotonin [68].

Since fenfluramine has been extensively studied with an increasing use of individual enantiomers, much can be learned about entactogens by comparing their effects with those of fenfluramine. An interesting example of this can be found in studies with cocaine, which, compared with (+)-amphetamine, may produce stimulus effects that are more MDMA-like. Broadbent et al. [51] reported that neither isomer of MDA substituted for (+)-amphetamine, but (+)-MDA and, to a lesser extent, (−)-MDA substituted for cocaine. As a test drug, cocaine completely substitutes for MDA [15] and MDMA but only partially substitutes for (+)-MBDB (Table 1) and fenfluramine [61].

The serotonergic properties of cocaine may account for some of these differences with (+)-amphetamine. White and Appel [61] found that fenfluramine-appropriate responding after cocaine was reduced by haloperidol and cyproheptadine. The data were interpreted to mean that cocaine partially mimicked fenfluramine through a serotonergic mechanism secondary to dopamine stimulation. Cocaine's ability to increase synaptic serotonin levels may lead to a greater similarity between its effects and those of MDA, MDMA, MBDB [39, 40], and fenfluramine [66–68]. Thus cocaine may be able to completely substitute for drugs such as MDA and MDMA, which share its serotonergic actions *and* some of its dopaminergic activity. Partial substitutions may result with compounds such as (+)-MBDB and fenfluramine, which share with cocaine the former but not the latter.

Given the apparent similarities between the in vivo and in vitro effects of fenfluramine and entactogens in rats, this would seem to imply that the

dioxole ring is not essential. However, as previously mentioned, the psychopharmacology of fenfluramine is quite different from that of MDMA. While MDMA produces CNS stimulation and euphoria, fenfluramine, in common doses, is sedative and dysphoric. A detailed comparison of the pharmacology of fenfluramine and MDMA may be necessary before we understand exactly how MDMA works.

Other similarities between (+)-MBDB and fenfluramine include the partial substitution of the selective serotonin uptake inhibitor fluoxetine [61]. In addition, the serotonin antagonists cyproheptadine and methiothepin decreased fenfluramine-appropriate responding from 95% to 30% [61]. Pretreatment in (+)-MBDB-trained rats with the serotonin antagonist metergoline demonstrated a similar effect. More detailed studies with other serotonin antagonists will be necessary before conclusions may be reached. Table 3 summarizes the results of attempts to block the training cue in (+)-MBDB-trained rats.

Based on the modest ability of the (+)-isomers of MDMA and MBDB to inhibit the reuptake of norepinephrine into hypothalamic synaptosomes [39], it seemed possible that noradrenergic pathways might be involved in the cue. In another series of drug discrimination experiments designed to test this hypothesis, the specific norepinephrine uptake inhibitor (−)-tomoxetine [69] was tested for stimulus transfer in doses up to 10 mg/kg in MDMA-trained rats. At 5 mg/kg, 67% of the animals responded on the drug lever, indicating that some similarity in pharmacology may exist. However, pretreatment with tomoxetine of six rats trained to discriminate MDMA from saline had no effect on discrimination of a subsequent dose of MDMA. One may anticipate that, eventually, appropriate pharmacological manipulations will be found that will give useful information about the mechanism of action for entactogens.

5.4. PCA — the 4-Cl substituent

One might also speculate that para-chloroamphetamine (PCA, 14) would have an effect similar to MDMA. Indeed, the early clinical data for PCA suggest that it possessed antidepressant activity [70]. This would suggest that the human psychopharmacology of PCA may well be closer to that of MDMA than is fenfluramine, but it is unlikely that clinical experiments can be carried out to study this. In drug discrimination studies, PCA substitutes for both a low dose [61] and a high dose [63] of fenfluramine but has not yet been tested in entactogen-trained animals.

5.5. PMA — the 4-methoxy substituent

In another study underway in our laboratory, we have begun to examine the effect of para-methoxyamphetamine (PMA, 15) in MDMA-trained rats. Complete substitution of PMA for MDMA would be consistent with a mechanism of action for MDMA where serotonin release is important, since PMA is a potent releasing agent of serotonin both in vivo [71] and in vitro

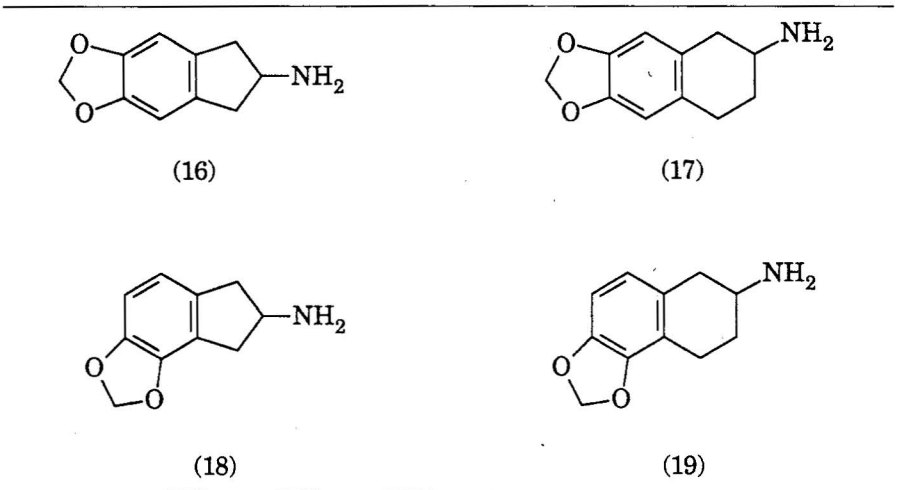


Figure 9.

[41, 72]. PMA also is a potent releaser of norepinephrine in peripheral tissues [73], but the blockade of its behavioral effects by chlorimipramine [71] suggests that serotonin release may be important in the mechanism of action. PMA did make a brief appearance on the illicit market in the early 1970s but was responsible for several deaths [74], and its use subsequently declined.

5.6. Rigid analogues

Most recently, the tetralin and indan analogues of MDA (16–19, Figure 9) have been examined. It has been previously shown that when hallucinogenic amphetamine derivatives are incorporated into similar structures, the hallucinogen-like activity in animal models is lost [75]. Thus, one might anticipate that a similar strategy with MDMA could lead to congeners that would lack MDA-like hallucinogenic effects. Furthermore, by examination of the two methylenedioxy positional isomers, one could infer the binding conformation of MDMA itself at the target site. As shown in Table 4, one positional isomer is clearly preferred for MDMA-like activity.

Furthermore, the indan derivative 16 substitutes for MDMA with a potency at least comparable to that of the training drug and was more potent than MDMA in substituting for (+)-MBDB. When administered to (+)-amphetamine-trained rats, compound 16 failed to elicit a drug lever choice from a single rat out of 29 tested at four doses. Together with a lack of substitution for LSD, the data indicate that this compound provides a good example of a drug that can potently mimic both MDMA and MBDB, while at the same time showing significant differences from hallucinogenic and stimulant training drugs.

Table 4. Drug discrimination results of substitution tests of rigid analogues of MDA in rats trained to discriminate MDMA (1.75 mg/kg) from saline.

Structure no.	ED_{50} (μmol/kg) and 95% confidence interval
16	2.75 (1.61–4.69)
17	5.68 (3.31–9.73)
18	Partial substitution
19	Partial substitution

Thus, with this series, definition has begun for some of the conformational preferences of the receptor or target sites with which MDMA interacts, at least in producing its discriminative cue. The results of these studies have also been useful for contrasting stimulant and entactogen activities. When Glennon et al. [52] tested the unsubstituted analogues of 16 and 17 in (+)-amphetamine-trained rats, 2-aminotetralin reportedly had about twice the potency of 2-aminoindan, and it was concluded that the former compound best mimics the conformation of amphetamine for producing amphetamine-like stimulus effects. The results described above for 16–19 strongly suggest that MDMA-like drugs probably adopt a different active conformation at their target site than does amphetamine.

6. DIFFERENCES BETWEEN ENTACTOGENS AND HALLUCINOGENS

6.1. EEG studies

Recently, collaborative studies with Dr. W. Dimpfel have been employed using quantitative radioelectroencephalography in the rat to characterize the EEG "fingerprint" of hallucinogenic amphetamines and of MDMA and MBDB. With this technique, four bipolar stainless steel electrodes are chronically implanted in each of four brain regions in rats: frontal cortex, hippocampus, striatum, and reticular formation [76]. The rats are freely-moving, and transmission of field potentials is accomplished using a telemetric device. The EEG is analyzed by Fourier analysis. Power density spectra are computed for periods of four seconds, are segmented into six frequency bands, and are averaged on each channel over time blocks of 15 minutes.

Using this method, a variety of hallucinogenic and non-hallucinogenic compounds were examined. As previously reported [77], hallucinogens produce a marked increase of power in the α_1 frequency (7.0–9.50 Hz) in the striatum. The ability to increase power in this region of the EEG has been observed for other classes of serotonergic drugs, including the 5-HT_{1A} agonists ipsapirone, gepirone, and buspirone, and with serotonin uptake inhibitors [78]. However, with 5-HT_{1A} agonists, an increase in α_1 power is recorded only from the frontal cortex and hippocampus.

Doses of DOM, DOB, or DOI of 0.2, 0.1, and 0.1 mg/kg, respectively, produced a pronounced and long-lasting increase in α_1 power recorded from the striatum. By contrast, doses of (+)-MDMA and (+)-MBDB up to 1.6

mg/kg did not elicit this characteristic feature in the EEG. Thus in this sensitive, quantitative EEG procedure, neither MDMA nor MBDB elicited an EEG "fingerprint" (four electrodes x six frequency bands per electrode) that resembled the fingerprint produced by the hallucinogenic amphetamines DOM, DOB, or DOI, or by LSD. These data are consistent with the results obtained in other models and further support the hypothesis that MDMA and MBDB cannot be classified as hallucinogenic phenethylamines.

6.2. Summary of structure-activity relationship differences

There are four structural features that currently contrast the structure-activity relationships of entactogens with those of hallucinogenic amphetamines.

1. Ring substitution at only the 3,4- positions does not give active hallucinogens, except for MDA. However, this substitution is active for entactogenic agents.
2. N-methylation greatly attenuates hallucinogenic activity but has no significant effect on potency of entactogens. N-ethylation also seems to allow compounds to retain entactogenic activity.
3. The more active stereochemistry of the entactogens is *S*, while that of the hallucinogenic amphetamines is *R*.
4. Extension of the alpha-methyl to an alpha-ethyl abolishes hallucinogenic activity but only has a minor effect on entactogens.

At the present time these contrasts seem sufficient to distinguish between the two drug classes. The stereochemical argument and the effects of alpha-ethylation are extremely powerful.

7. DIFFERENCES BETWEEN ENTACTOGENS AND STIMULANTS

There are several lines of evidence that distinguish entactogens from stimulants. The drug discrimination data are consistent with the view that although the dopaminergic activity of MDA and MDMA may account for similarities observed with stimulants, depending on the experimental conditions, their primary pharmacological activity is similar to that of MBDB and is probably related to effects in serotonin pathways.

Although amphetamine substitutes for MDMA in our studies, this only occurs at doses that disrupt a significant number of animals, indicative of a partially overlapping profile of action [7]. Furthermore, the large ED_{50} for amphetamine substitution in MDMA-trained rats is certainly not consistent with the known potency of amphetamine in measures of its stimulant activity. That is, in humans or in animal assays of its activity as a CNS stimulant, amphetamine is perhaps ten times more potent than MDA or MDMA. Thus its large ED_{50} in MDA-trained or MDMA-trained rats, relative to that of the enantiomers of MDA or MDMA, seems to suggest strongly that the primary discriminative cue of MDMA cannot simply be "amphetamine-like."

In animals trained to discriminate (+)-amphetamine from saline, some investigators have reported stimulus transfer with MDMA. In our paradigm, no substitution occurred. Differences in experimental design or in numbers of animals and doses tested may account for this discrepancy. Thus, in our experiments, symmetrical transfer did not occur between MDMA and amphetamine. The MDMA cue certainly seems complex and may have some similarity to amphetamine. However, suggestions that the pharmacology of MDMA is essentially the same as that of amphetamine are clearly not warranted by the data.

In summary, the following points highlight the differences between entactogens and stimulants.

1. The primary pharmacological effects of entactogens are serotonergically, not dopaminergically, mediated. This is clearly indicated by the lack of stimulant-related activity for MBDB, which can be attributed to the ability of an alpha-ethyl substituent on phenethylamines to attenuate potency at presynaptic dopamine release sites. Further evidence is provided by the ability of metergoline to block (+)-MBDB, the inability of haloperidol to block the cues produced by either MDMA or (+)-MBDB, and by the similarity between (+)-MBDB and the serotonergic drug fenfluramine.
2. A stimulant component is not necessary for entactogen activity. Drugs such as fenfluramine, MDE, 2,3-MDA, and (16) substitute for entactogens but do not substitute for (+)-amphetamine.
3. The active conformation of the side chains of MDMA and amphetamine are probably different, as indicated by the relative potencies of their respective aminoindan and aminotetralin analogues.
4. The stereo*selective* activity of entactogens in entactogen-trained animals contrasts with the stereo*specific* activity when generalization occurs in (+)-amphetamine substitution tests. Although entactogens and stimulants display similar stereoselectivity, when tested within their respective classes, the *R* isomers of MDA, MDMA, and MBDB substitute for MDMA and (+)-MBDB but not for (+)-amphetamine. In fact, contrary to other estimates of potency, the *R* isomer of MDA is more potent than the *S* isomer of amphetamine in substituting for MDMA.
5. The effects on stimulant and entactogen activities differ for N-ethyl and N-OH substitutions.
6. N-methylation leads to increased toxicity for amphetamine but decreased toxicity for MDA.

8. OUTLOOK FOR THE FUTURE

If entactogens are a distinct pharmacological class, the next question must concern the therapeutic utility of such novel agents. The term entactogen was chosen [1] after a consideration of the potential therapeutic applications of the drug class it described. The name is meant to apply to agents with MDMA-

like pharmacology, but would generally apply to any substance that can produce (gen) an inner (en) "touching" (tact).

Just as the word tact, with the same Latin root tactus, is meant to imply both skill and considerateness in dealing with others and the ability to do or say the appropriate thing, entactogens should ideally produce an inner state where the patient does not feel threatened or defensive. Yet, the memory cannot be dulled as it is with benzodiazepines. Indeed, memory retrieval should be facilitated, so that the ability to recall emotionally painful, repressed memories is not impaired.

Since the neurochemistry of anxiety, depression, and other basic emotional states has not yet been elucidated, it may be quite some time before the pharmacology of entactogens is fully understood. Nevertheless, when a drug like MDMA produces a unique psychoactive effect, it should be possible, given enough time, to gain an understanding of the neuronal substrates that mediate its effect(s).

The serotonin neurotoxicity of MDA and MDMA has resulted in the need to develop new compounds that may retain clinical utility but be devoid of potentially harmful side effects. Is it possible that non-neurotoxic entactogens can be developed? As with most technologies, this is a two-edged sword. A major concern might be that a non-neurotoxic entactogen could become popular as a recreational drug. Although the possibility of neurotoxicity with MDMA should be a deterrent to potential users of this drug, it is not clear that this knowledge has had any effect on MDMA abuse. Even if a nontoxic entactogen were abused to the same extent as MDMA, at least concerns over neurological damage would be lessened. On the other hand, if clinical utility exists for MDMA-like substances, it cannot be explored until the issue of neurotoxicity is resolved. Hence, a non-neurotoxic MDMA congener would perhaps allow clinical testing of the potential of these compounds as adjuncts to psychotherapy. Should such drugs be proven efficacious for this use, the significance of this advance for psychiatry would far outweigh any concerns about abuse of entactogens.

Non-neurotoxic entactogens can and will be discovered. Sufficient evidence already exists to support this hypothesis. For example, Schechter [24] has shown that the discriminative stimulus properties of MDMA are largely dissipated by four hours following drug administration. On the other hand, Schmidt [79] found that MDMA has a biphasic depleting effect on cortical serotonin, with the later phase (>6 hours) associated with the long term toxicity and blocked by fluoxetine.

Schmidt and Taylor [80] administered the serotonin uptake inhibitor fluoxetine to rats three hours after treatment with MDMA and were able to prevent neurotoxicity. These workers suggested that the unique neurochemical effects of MDMA are independent of the long-term neurotoxicity. In our studies, it was shown that fluoxetine does not antagonize the MDMA discriminative cue. Battaglia et al. [81] reported that acute MDMA treatment decreased brain

serotonin and 5-HIAA levels, but that multiple MDMA treatments were required to decrease the number of 5-HT uptake sites, the latter response presumably a reflection of neuron terminal degeneration. All these studies indicate that the acute pharmacology of MDMA can be dissociated from the long-term neurotoxic effects.

Further, it is also known from work with the neurotoxin para-chloroamphetamine that some structural congeners have an acute 5-HT depleting effect on brain 5-HT but lack the long-term neurotoxicity that is characteristic of PCA [82]. Since the psychopharmacological effects of MDMA have a relatively rapid onset and in rodents are largely dissipated at a time when a serotonin uptake inhibitor can still block neurotoxicity, it seems quite clear that molecules can be developed that will probably possess human psychopharmacology similar to MDMA but will lack serotonin neurotoxicity. When this is accomplished, we can look forward to a clear definition of the primary pharmacology of entactogens, and one would hope that at that time clinical studies with such a compound would be possible to determine, finally, whether entactogens represent a new technology for psychiatry.

ACKNOWLEDGEMENT

This research was supported in part by USPHS grants DA-02189 and DA-04758 from the National Institute on Drug Abuse and Biomedical Research Support Grant 2-507-RR05586-18.

REFERENCES

1. Nichols, D.E., Hoffman, A.J., Oberlender, R.A., Jacob III, P., and Shulgin, A.T., 1986. Derivatives of 1-(1,3-benzodioxol-5-yl)-2-butanamine: Representatives of a novel therapeutic class. J. Med. Chem. 29:2009–2015.
2. Nichols, D.E., 1986. Differences between the mechanisms of action of MDMA, MBDB, and the classical hallucinogens. Identification of a new therapeutic class: Entactogens. J. Psychoactive Drugs 18:305–313.
3. Oberlender, R. and Nichols, D.E., 1988. Drug discrimination studies with MDMA and amphetamine. Psychopharmacology 95:71–76.
4. Jaffe, J.H., 1985. Drug addiction and drug abuse. In *The Pharmacological Basis of Therapeutics*, Seventh Edition, (Gilman, A.G., Goodman, L.S., Rall, T.W., Murad, F. eds). New York: Macmillan Publishing Company, pp. 523–581.
5. Weiner, N., 1980. Norepinephrine, epinephrine, and the sypathomimetic amines. In *The Pharmacological Basis of Therapeutics*, Sixth Edition, (Gilman, A.G., Goodman, L.S. and Gilman, A., eds.) New York: Macmillan, pp. 138–175.
6. Greer, G. and Tolbert, R., 1986. Subjective reports of the effects of MDMA in a clinical setting. J. Psychoactive Drugs 18:319–327.
7. Stolerman, I.P. and D'Mello G.D., 1981. Role of training conditions in discrimination of central nervous system stimulants by rats. Psychopharmacology 73:295–303.
8. Barry, H., 1974. Classification of drugs according to their discriminable effects in rats. Fed. Proc. 33:1814–1824.
9. Overton, D.A., (1984). State dependent learning and drug discriminations. In *Handbook of Pyschopharmacology*, Vol. 18 (Iversen, L.L., Iversen, S.D. and Snyder, S.H., eds.) New York: Plenum Press, pp. 59–126.
10. Weil, A., 1976. The love drug. J. Psychoactive Drugs 8:335–337.
11. Turek, I.S., Soskin, R.A., and Kurland, A.A., 1974. Methylenedioxyamphetamine (MDA). Subjective effects. J. Psychedelic Drugs 6:7–14.

12. Shannon, H.E., 1980. MDA and DOM: Substituted amphetamines that do not produce amphetamine-like discriminative stimuli in the rat. Psychopharmacology 67:311–312.
13. Glennon, R.A., Rosecrans, J.A., and Young, R., 1981. Behavioral properties of psychoactive phenylisopropylamines in rats. Eur. J. Pharmacol. 76:353–360.
14. Glennon, R.A., Young, R., Rosecrans, J.A., and Anderson, G.M., 1982. Discriminative stimulus properties of MDA analogues. Biol. Psychiat. 17:807–814.
15. Glennon, R.A. and Young, R., 1984. MDA: An agent that produces stimulus effects similar to those of 3,4-DMA, LSD and cocaine. Eur. J. Pharmacol. 99:249–250.
16. Glennon, R.A. and Young, R., 1984. MDA: A psychoactive agent with dual stimulus effects. Life Sci. 34:379–383.
17. Shulgin, A.T., 1978. Psychotomimetic drugs: Structure-activity relationships. In *Handbook of Psychopharmacology*. Vol. 11 (Iversen, L.L., Iversen, S.D. and Snyder, S.H., eds.). New York: Plenum, pp. 243–333.
18. Jackson, B. and Reed Jr, A. 1970. Another abusable amphetamine. JAMA 211:830.
19. Yensen, R., DiLeo, F.B., Rhead, J.C., Richards, W.A., Soskin, R.A., Turek, B., and Kurland, A.A., 1974. MDA-Assisted psychotherapy with neurotic outpatients: A pilot study. J. Nerv. Ment. Dis. 163:233–245.
20. Naranjo, C., Shulgin, A.T., and Sargent, T., 1967. Evaluation of 3,4-methylenedioxyamphetamine (MDA) as an adjunct to psychotherapy. Med Pharmacol. Exp. 17:359–364.
21. Shulgin, A.T. and Nichols, D.E., 1978. Characterization of three new psychotomimetics. In *The Psychopharmacology of Hallucinogens* (Stillman, R.C. and Willette, R.E., eds). New York: Pergamon, pp. 74–83.
22. Siegel, R.K., 1986. MDMA: Nonmedical use and intoxication. J. Psychoactive Drugs 18:349–354.
23. Glennon, R.A. and Young, R., 1984. Further investigation of the discriminative stimulus properties of MDA. Pharmacol. Biochem. Behav. 20:501–505.
24. Schechter, M.D., 1986. Discriminative profile of MDMA. Pharmacol. Biochem. Behav. 24:1533–1537.
25. Evans, S.M. and Johanson, C.E., 1986. Discriminative stimulus properties of (±)-3,4-methylenedioxymethamphetamine, and (±)-3,4-methylenedioxyamphetamine in pigeons. Drug Alc. Depend. 18:159–164.
26. Kamien, J.B., Johanson, C.E., Schuster, C.R., and Woolverton, W.L., 1986. The effects of (±)-methylenedioxymethamphetamine and (±)-methylenedioxyamphetamine, in monkeys trained to discriminate (+)-amphetamine from saline. Drug Alc. Depend. 18:139–147.
27. Boja, J.W. and Schechter, M.D., 1987. Behavioral effects of N-ethyl-3,4-methylenedioxyamphetamine (MDE; "Eve"). Pharmacol. Biochem. Behav. 28:153–156.
28. Braun, U., Shulgin, A.T., and Braun, G., 1980. Centrally active N-substituted analogs of 3,4-methylenedioxyphenylisopropylamine (3,4-methylenedioxyamphetamine). J. Pharm. Sci. 69:192–195.
29. Fuller, R.W., Perry, K.W., Baker, J.C., Parli, C.J., Lee, N., Day, W.A., and Molloy, B.B., 1974. Comparison of the oxime and the hydroxylamine derivatives of 4-chloroamphetamine as depletors of brain 5-hydroxyindoles. Biochem. Pharmacol. 23:3267–3272.
30. Glennon, R.A., Yousif, M., and Patrick, G., 1988. Stimulus properties of 1-(3,4-methylenedioxyphenyl)-2-aminopropane (MDA) analogs. Pharmacol. Biochem. Behav. 29:443–449.
31. Noggle Jr, F.T., DeRuitter, J., Coker, S.T., and Clark, C.R., 1987. Synthesis, identification, and acute toxicity of some N-alkyl derivatives of 3,4-methylenedioxyamphetamine. J. Assoc. Off. Anal. Chem. 70:981–986.
32. Hardman, H.F., Haavik, C.O., and Seevers, M.H., 1973. Relationship of the structure of mescaline and seven analogs to toxicity and behavior in five species of laboratory animals. Toxicol. App. Pharmacol. 25:299–309.
33. Shulgin, A.T., 1980. Hallucinogens. In *Burger's Medicinal Chemistry*, Fourth Edition (Wolff, M.E., ed.). New York: Wiley-Interscience, pp. 1109–1137.
34. Standridge, R.T., Howell, H.G., Gylys, J.A., Partyka, R.A., and Shulgin, A.T., 1976. Phenylalkylamines with potential psychotherapeutic utility. 1. 2-Amino-1-(2,5-dimethoxy-4-methylphanyl) butane. J. Med. Chem. 19:1400–1404.
35. Winter, J.C., 1980. Effects of the Phenethylamine Derivatives, BL-3912, Fenfluramine, and Sch-12679, in rats trained with LSD as a Discriminative Stimulus. Psychopharmacology 68:159–162.

36. Beardsley, P.M., Balster, R.L., and Harris, L.L., 1986. Self-administration of methylenedioxymethamphetamine (MDMA) by rhesus monkeys. Drug Alc. Depend. 18:149–157.
37. Lamb, R.J. and Griffiths, R.R., 1987. Self-injection of d,1–3,4-methylenedioxymethamphetamine in the baboon. Psychopharmacology 91:268–272.
38. Wise, R.A. and Bozarth, M.A., 1987. A psychomotor stimulant theory of addiction. Psychol. Rev. 94:469–492.
39. Steele, T.D., Nichols, D.E., and Yim, G.K.W., 1987. Stereochemical effects of 3,4-methylenedioxymethamphetamine (MDMA) and related amphetamine derivatives on inhibition of uptake of [^{3}H]-monoamines into synaptosomes from different regions of rat brain. Biochem. Pharmacol. 36:2297–2303.
40. Johnson, M.P., Hoffman, A.J., and Nichols, D.E., 1986. Effects of the enantiomers of MDA, MDMA and related analogs on [^{3}H]serotonin and [^{3}H]dopamine release from superfused rat brain slices. Eur. J. Pharmacol. 132:269–276.
41. Nichols, D.E., Lloyd, D.H., Hoffman, A.J., Nichols, M.B., and Yim, G.K.W., 1982. Effects of certain hallucinogenic amphetamine analogues on the release of [^{3}H]serotonin from rat brain synaptosomes. J. Med. Chem. 25:530–535.
42. Nichols, D.E. and Glennon, R.A., 1984. Medicinal chemistry and structure-activity relationships of hallucinogens. In *Hallucinogens: Neurochemical, Behavioral, and Clinical Perspectives* (Jacobs, B. ed.). New York: Raven Press, pp. 95–142.
43. Anderson III, G.M., Braun, G., Braun, U., Nichols, D.E., and Shulgin, A.T., 1978. Absolute configuration and psychotomimetic activity. In *QuaSAR Quantitative Structure Activity Relationships of Analgesics, Narcotic Antagonists, and Hallucinogens* (Barnett, G., Trsic, M. and Willette, R.E., eds). National Institute on Drug Abuse Research Monograph 22. DHEW Pub. No. (ADM) 78–729. Washington, DC: Supt of Documents, U.S. Government Printing Office, pp. 27–32.
44. Schechter, M.D., 1987. MDMA as a discriminative stimulus: Isomeric comparisons. Pharmacol. Biochem. Behav. 27:41–44.
45. Glennon, R.A., Titeler, M., and Young, R., 1986. Structure-activity relationships and mechanism of action of hallucinogenic agents based on drug discrimination and radioligand binding studies. Psychopharmacol. Bull. 22:953–958.
46. Appel., J.B. and Cunningham, K.A., 1986. The use of drug discrimination procedures to characterize hallucinogenic drug actions. Psychopharmacol. Bull. 22:959–969.
47. Lyon, R.A., Glennon, R.A., and Titeler, M., 1986. 3,4-Methylenedioxymethamphetamine (MDMA): Stereoselective interactions at brain 5-HT_1 and 5-HT_2 receptors. Psychopharmacology 88:525–526.
48. Rosecrans, J.A. and Glennon, R.A., 1987. The effect of MDA and MDMA ("ecstasy") isomers in combination with pirenpirone on operant responding in mice. Pharmacol. Biochem. Behav. 28:39–42.
49. Callahan, P.M. and Appel, J.B., 1987. Differences in the stimulus properties of 3,4-methylenedioxyamphetamine (MDA) and N-Methyl-1-(3,4-methylenedioxyamphetamine) (MDMA) in animals trained to discriminate hallucinogens from saline. Soc. Neurosci. Abst., p. 1720 (476.2).
50. Trulson, M.E., Crisp, T., and Henderson, L.J., 1983. Mescaline elicits behavioral effects in cats by action at both serotonin and dopamine receptors. Eur. J. Pharmacol. 96:151–154.
51. Broadbent, J., Michael, E.K., Ricker, J.H., and Appel, J.B., 1987. A comparison of the discriminative stimuli of (+) and (−)-3,4-methylenedioxyamphetamine (MDA) with those of hallucinogenic and stimulant drugs. Soc. Neurosci. Abstract, p. 1720 (476.1).
52. Glennon, R.A., Young, R., Hauck, A.E., and McKenney, J.D., 1984. Structure-activity studies on amphetamine analogues using drug discrimination methodology. Pharmacol. Biochem. Behav. 21:895–901.
53. Young, R. and Glennon, R.A., 1986. Discriminative stimulus properties of amphetamine and structurally related phenalkylamines. Med. Res. Rev. 6:99–130.
54. Ariëns, E.J., 1987. Stereochemistry in the analysis of drug action. Part II. Med. Res. Rev. 7:367–387.
55. Glennon, R.A., Young, R., and Soine, W., 1984. 1-(2,3-Methylenedioxyphenyl)-2-aminopropane (2,3-MDA): A preliminary investigation. Gen. Pharmacol. 15:361–362.
56. Glennon, R.A., Yousif, M., Naiman, N., and Kalix, P., 1987. Methcathinone: A new and potent amphetamine-like agent. Pharmacol. Biochem. Behav. 26:547–551.

57. Beregi, L.G., Hugon, P., LeDouarec, J.C., Laubie, M., and Duhault, J., 1970. Structure-activity relationships in CF_3 substituted phenethylamines. in *Amphetamines and Related Compounds* (Costa, E. and Garattini, S. eds.). New York: Raven Press, pp. 21–61.
58. Woodward Jr, E., 1970. Clinical experience with fenfluramine in the United States. In *Amphetamines and Related Compounds* (Costa, E. and Garattini, S., eds). New York: Raven Press, pp. 21–61.
59. Griffith, J.D., Nutt, J.G., and Jasinski, D.R., 1975. A comparison of fenfluramine and amphetamine in man. Clin. Parmacol. Ther. 18:563–570.
60. Chait, L.D., Uhlenhuth, E.H., and Johanson, C.E., 1986. The discriminative stimulus and subjective effects of d-amphetamine, phenmetrazine and fenfluramine in humans. Psychopharmacology 89:301–306.
61. White, F.J. and Appel, J.B., 1981. A Neuropharmacological analysis of the discriminative stimulus properties of fenfluramine. Psychopharmacology 73:110–115.
62. Goudie, A.J., 1977. Discriminative stimulus properties of fenfluramine in an operant task: An analysis of its cue function. Psychopharmacology 53:97–102.
63. McElroy, J.F. and Feldman, R.S., 1984. Discriminative stimulus properties of fenfluramine: Evidence for serotonergic involvement. Psychopharmacology 83:172–178.
64. Colpaert, F.C., Niemergeers, C.J.E., and Janssen, P.A.J., 1978. Discriminative stimulus properties of cocaine and d-amphetamine, and antagonism by haloperidol: A comparative study. Neuropharmacolology 17:937–942.
65. Invernizzi, R., Berettera, C., Garattini, S., and Samanin, R., 1986. D- and L-isomers of fenfluramine differ markedly in their interaction with brain serotonin and catecholamines in the rat. Eur. J. Pharmacol. 120:9–15.
66. Borroni, E., Ceci, A., Garattini, S., and Mennini, T., 1983. Differences between d-fenfluramine and d-norfenfluramine in serotonin presynaptic mechanisms. J. Neurochem. 40: 891–893.
67. McElroy, J.F., DuPont, A.F., and Feldman, R.S., 1982. The effects of fenfluramine and fluoxetine on the acquisition of a conditioned avoidance response in rats. Psychopharmacology 77:356–359.
68. Fuller, R.W., Snoddy, H.D., and Robertson, D.W., 1988. Mechanisms of effects of d-fenfluramine on brain serotonin metabolism in rats: Uptake inhibition versus release. Pharmacol. Biochem. Behav. 30:715–721.
69. Wong, D.T., Threlkeld, P.G., Best, K.L., and Bymaster, F.P., 1982. A new inhibitor of norepinephrine uptake devoid of affinity for receptors in rat brain. J. Pharmacol. Exp. Ther. 222:61–65.
70. Verster, J. and Van Prag, H.M., 1970. A comparative investigation of methylamphetamine and 4-chloro-N-methylamphetamine in healthy test subjects. Pharmako-Psychiatrie Neuro-psychopharmacologie. 3:239–248.
71. Tseng, L–F, Harris, R.A., and Loh, H.H., 1978. Blockade of para-Methoxyamphetamine-induced serotonergic effects by chlorimipramine. J. Pharmacol. Exp. Ther. 204:27–38.
72. Tseng, L–F, Menon, M.K., and Loh, H.H., 1976. Comparative actions of monomethoxy-amphetamines on the release and uptake of biogenic amines in brain tissue. J. Pharmacol. Exp. Ther. 197:263–271.
73. Cheng, H.C., Long, J.P., Nichols, D.E., and Barfknecht, C.F. 1974. Effects of para-methoxyamphetamine (PMA) on the cardiovascular system of the dog. Arch. Int. Pharmacodyn. Ther. 212:83–88.
74. Cimbura, G. 1974. PMA Deaths in Ontario. Can. Med. Ass. J. 110:1263–1265.
75. Nichols, D.E., Barfknecht, C.F., Long, J.P., Standridge, R.T., Howell, H.G., Partyka, R.A., and Dyer, D.C., 1974. Potential psychotomimetics 2: Rigid analogs of 2,5-Dimethoxy-4-methylphenylisopropylamine (DOM, STP). J. Med. Chem. 17:161–166.
76. Dimpfel, W., Spüler, M., Nickel, B., and Tibes, U., 1986. "Fingerprints" of Central Stimulatory Drug Effects by Means of Quantitative Radioelectroencephalography in the Rat (Tele-Stereo-EEG). Neuropsychobiology 15:101–108.
77. Spüler, M. and Nichols, D.E., 1988. Effects of the hallucinogenic drugs LSD, DOM and Scopolamine on the frequency content of field potentials from the rat brain (Tele-Stereo-EEG). Deutsch Gesellschaft für Pharmakologie and Toxikologie., Abstract 451.
78. Dimpfel, W., Spüler, M., Traber, J., and Nichols, D.E., 1988. Tele-Stereo-EEG in the rat after injection of drugs interacting with serotonergic transmission. Intl. Pharmacol. EEG

Group Symposium, Abstracts, Kobe, Japan.
79. Schmidt, C.J., 1987. Neurotoxicity of the psychedelic amphetamine, methylenedioxymethamphetamine. J. Pharmacol. Exp. Ther. 240:1–7.
80. Schmidt, C.J. and Taylor, V.L., 1987. Acute Effects of methylenedioxymethamphetamine (MDMA) on 5-HT synthesis in the rat brain. Pharmacologist 29:(224).
81. Battaglia, G., Yeh, S.Y., and DeSouza, E.G., 1988. MDMA-Induced neurotoxicity: Parameters of degeneration and recovery of brain serotonin neurons. Pharmacol. Biochem. Behav. 29:269–274.
82. Fuller, R.W., Wong, D.T., Snoddy, H.D., and Bymaster, F.P., 1977. Comparison of the effects of 6-chloro-2-aminotetralin and of Org 6582, a related chloroamphetamine analog, on brain serotonin metabolism in rats. Biochem. Pharmacol. 26:1333–1337.