Differences Between the Mechanism of Action of MDMA, MBDB, and the Classic Hallucinogens. Identification of a New Therapeutic Class: Entactogens

DAVID E. NICHOLS, PH.D.*

The widespread use of psychedelic drugs, such as lysergic acid diethylamide (LSD), during the 1960's and 1970's led to severe reactions by governmental agencies and proscriptions against their use. However, with the high degree of interest in mind-altering drugs in the United States, as evidenced by their widespread popularity, it was only a matter of time before new drugs appeared that were developed outside of the pharmaceutical companies.

Nearly 70 years after its first synthesis, 3,4-methylenedioxymethamphetamine (MDMA) was rediscovered. Although it had its more recent origin in the class of drugs that is generally defined as psychedelic or hallucinogenic, it clearly appears different from LSD. In humans, MDMA induces a state of reduced anxiety and lowered defensiveness that makes it attractive to therapists wishing to speed up the therapeutic process. However, as with all substances that produce pleasurable effects, it soon became popular as a recreational drug, and it went the same way as the psychedelics: into Schedule I.

The present author's interest in MDMA stems from longstanding efforts, spanning nearly 17 years, to understand how psychedelic substances work. In contrast to the pharmacologist, who often studies the effect of a single drug to understand how it works, the development of a potency-series is employed. That is, a series of drugs closely related in structure is prepared and the biological potency of the members of the series is measured. Then, with these numbers in hand, one attempts to develop quantitative structure-activity relationships (QSARs). Simply stated, attempts are made to find quantitative correlations (or equations) that relate biological activity to fundamental properties of the molecule. This approach is being widely developed in the pharmaceutical industry in order to understand more fully how particular types of drugs work, and to be able to predict which additional molecules should be synthesized. It should also be added that no equations have been developed that adequately correlate hallucinogenic or psychedelic activity with any particular molecular property.

In this context, it is important to define clearly the type of biological activity that is being measured. It is typical that if a molecule has several different sites of action in the brain, that each one of these actions may be related to entirely different structural features or properties of the molecule. Thus, to develop valid QSARs, one needs to measure some index of pure biological activity. It goes almost without saying that psychedelics probably do not have any one pure mechanism of action. That is, their complex array of behavioral effects is probably the net result of multiple neurochemical component processes. Martin and his colleagues (Nozaki, Vaupel & Martin 1977) at the Lexington (Kentucky) Addiction Research Center were probably the first strong proponents of this idea, but several later groups (including the present author's research team) have reiterated that these substances may all differ in the scope of their qualitative effects (Glennon & Young 1984a, 1984b, 1984c; Nichols et al. 1982). Some compounds have predominantly stimulant effects like amphetamine, while others have an action more like LSD or mescaline. In between, there is a whole

*Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907.

spectrum of biological action represented literally by a series of hundreds of molecules.

So, it is not entirely clear what is meant by the term "psychedelic" in the first place. It seems to be a catchall category that includes compounds that produce subjective effects in humans that resemble, *but only to varying degrees*, the effects produced by other compounds, such as LSD.

Within this context of mixed action, there is one substance that stands unique within the psychedelic category. This material is 3,4-methylenedioxyamphetamine (MDA). By and large, this drug does not produce profound sensory disruption or hallucinations (Naranjo, Shulgin & Sargent 1967). Of all the so-called, substituted amphetaminetype hallucinogens, MDA has remained popular and in high demand among recreational drug users. Although it does not generally produce hallucinations, it is unique because it powerfully enhances emotions and empathy. MDA earned a street reputation as the *love drug*, largely due to this latter quality (Thiessen & Cook 1973). During the effect of the drug, subjects experience a sense of amplified emotions, empathy and a powerful emotional bond with other persons present.

MDA has pharmacological properties, both in laboratory animals and in biochemical assays, that clearly distinguish it from hallucinogenic substances such as 2,5-dimethoxy-4-methylamphetamine (DOM, STP). From laboratory animal models, Martin and his colleagues have shown that MDA has effects similar to both LSD and amphetamine (Nozaki, Vaupel & Martin 1977). Moreover, when studies were carried out with the optical isomers of MDA, it was discovered that the LSD-like properties in animals were due to the effects of the levo-, or R-(−), isomer, while the effects of the dextro-, or S-(+), isomer were more like amphetamine (Nichols et al. 1986; Glennon & Young 1984a, 1984b, 1984c).

When a biologically active compound has two optical isomers, generally only one is active, or one is more active than the other. With all the other hallucinogens of the substituted amphetamine type, it is the levo-isomer that possesses the hallucinogenic activity (Nichols & Glennon 1984; Shulgin 1973). However, *both* isomers of MDA are active and their biological effects are different. There has been no other substituted hallucinogenic amphetamine studied where this has been found. The levo-isomer of MDA, while it produces some of the effects on emotion of the racemic mixture, is more similar to classic hallucinogens. Although the dextro-isomer is active at nearly the same dose, it is not like the hallucinogens, but does have an effect on emotion and empathy that is similar to racemic MDA (Shulgin 1978).

Against this background is the discovery of the effects of MDMA. Chemically, MDMA is simply the N-methyl derivative of MDA. However, this transformation has one pronounced effect: It attenuates or abolishes hallucinogenic activity. It is known from studies with other hallucinogenic amphetamines that the addition of a methyl group to the basic nitrogen is very detrimental to psychedelic activity (Shulgin 1978). In particular, because it is the levo-isomer of these compounds that is more biologically active, the effect of the N-methyl is to abolish the action of this isomer as a psychedelic. Nevertheless, MDMA is biologically active and has a potency of only slightly less than its parent, MDA. What is one to make of this finding? Either MDMA is not a hallucinogen or else it is a hallucinogen acting in a completely unexpected way that is different from the other substituted amphetamines.

Thus, one may see that the classification of MDA as a hallucinogen was based more on legal and enforcement concerns, than on animal or human pharmacology. Adding the N-methyl, which attenuates hallucinogenic activity in other compounds of this structural type, ought to abolish whatever residual hallucinogenic activity that MDA has, and one might expect MDMA to be nonhallucinogenic. In fact, MDMA does not have effects like LSD or DOM in rats (Nichols et al. 1986; Glennon et al. 1982), and human reports have indicated that MDMA does not produce hallucinatory effects (Anderson et al. 1978).

Nevertheless, because of concern by law enforcement agencies over the widespread popularity of MDMA as a recreational drug, it too seems to have been classified as a hallucinogen. It is not entirely clear how scheduling could have been carried out had MDMA somehow not been classified into an existing drug category. Indeed, some rather well-known scientists went as far as to call MDMA "just another hallucinogen" or "another LSD." However, there is no rational basis for such assessments.

Therefore, it was decided to test the hypothesis (in this author's laboratory) that MDMA and compounds with a related psychopharmacological action were completely different and belonged in an entirely new drug category. This hypothesis seemed reasonable for several reasons. First of all, MDA itself is really a unique compound among the so-called hallucinogens. It is not generally used for its hallucinogenic effect, but rather for its affect-enhancing qualities. One wonders whether it should be called a hallucinogen at all, based on its unusual pharmacology. Nevertheless, this uncertainty is the starting point for MDMA. One would expect that additional molecular changes that were known to abolish hallucinogenic activity in the substituted amphetamines would further remove MDMA-type compounds from the hallucinogenic category.

It was clear that MDMA had several features that set

it apart from the substituted amphetamine class of hallucinogens. First, as previously noted, it possesses the feature of N-methylation, which is known to attenuate activity in other amphetamine-type hallucinogens. In addition, and perhaps more important, is the fact that it is the dextro-isomer that proved to be more active (Anderson et al. 1978). This also contrasts with the amphetamine-type hallucinogens, where it is the levo-isomer that is more active.

There is a very fundamental assumption in pharmacology and medicinal chemistry that revolves around the concept of what is known as *three-point attachment*. Simply stated, it means that if a biological target receptor accommodates only one of two possible mirror image isomers (i.e., enantiomers) of a substance, there are a minimum of three points of interaction between the drug and its receptor. This occurs in a reliable and reproducible way for all drugs that have a high affinity for that receptor. This structurally well-defined receptor does not suddenly *decide* to accept the dextro-isomer for one compound, when for all other members of a drug series it prefers the levo-isomer. This fact alone is a powerful argument that MDMA cannot be interacting with the same target site or receptor that is involved in the action of hallucinogenic amphetamines, such as DOM. Indeed, Lyon, Glennon and Titeler (1986) have recently examined the ability of MDMA to bind to the serotonin 5-HT_2 receptor in rat brain. As expected, it was the levo-isomer of MDMA that bound with higher affinity, as did the levo-isomer of the hallucinogenic amphetamine DOM.

However, these arguments may still leave some clouds of doubt. To the layperson's view, the arrangement of atoms in MDMA *looks* very much like that in the hallucinogenic amphetamines. Therefore, additional structural modifications that could be made were considered, which might move MDMA derivatives even further from any logic that could label them as hallucinogenic.

It has been known for about 20 years—as first demonstrated by Shulgin (1963)—that if one extends the α-methyl of the hallucinogenic amphetamines to an α-ethyl, *all* hallucinogenic activity is lost. This is exemplified in the structures of Figure 1, where the active R enantiomer of DOM is compared with its α-ethyl compound BL-3912A (Standridge et al. 1976). Whereas DOM is hallucinogenic in oral doses from five to 10 mg, BL-3912A has been given to humans at doses up to 270 mg without producing hallucinogenic effects (Winter 1980). This is rather remarkable and attests to the powerful effect the α-ethyl group has in abolishing hallucinogenic activity.

It was readily apparent that the corresponding α-ethyl homologue of MDMA should be examined. When this author's research team first conceived of this, there was no way to know what effect this would have on the activity of this molecule. It was predicted, however, that this molecule would *not* be hallucinogenic.

This molecule (shown in Figure 1), N-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine (MBDB), was synthesized and tested. Dr. Peyton Jacob (working in collaboration with Dr. Alexander Shulgin) had also prepared this compound, but the rationale for its design had been developed from a somewhat different perspective. As a consequence, a collaborative effort was made to perform a fairly complete study of this substance, examining its effects in humans, rats and in a variety of biochemical pharmacology assays (Nichols et al. 1986; Steele, Nichols & Yim 1986). Although less potent than MDMA, MBDB had qualitative effects in humans very similar to MDMA. Furthermore, it was the dextro-isomer that was more active, similar to MDA and in contrast to the hallucinogenic amphetamines. In rats trained to discriminate LSD from saline, MBDB did *not* have LSD-like actions.

MBDB represents a structure that combines two separate structural features that abolish or attenuate hallucinogenic activity: N-methylation and α-ethylation. All logic of structure-activity relationships derived for substituted amphetamines argues that the synergistic attenuation provided by these two structural features should render MBDB totally inert as a hallucinogen. Yet, MBDB *is* biologically active. It generally has the same effect on emotion and empathy as does MDMA. Clearly, one is not dealing with the pharmacology of hallucinogens anymore, but with some different category of psychoactive drug.

Inasmuch as MBDB represented the first molecular structure that could definitely be placed outside the structure-activity definitions of the hallucinogenic amphetamine class, it was designated as the prototype of a new pharmacological class. This is not to say that MDMA—or even MDA—do not exert this same action to some degree, but only that MBDB is the clearest example, based on structure-activity relationship arguments, of a compound that cannot be classified as a hallucinogen. At this point, this author's research team felt it was justified to name this new category.

The term "empathogen" has been suggested as a name for drugs such as MDMA. However, this term was rejected for several reasons. First of all, MBDB or MDMA do more than simply generate empathy, the connotation of the term. Second, people invariably dislike hearing the word "pathogen," which clearly stands out when empathogen is pronounced. Because it was felt that these drugs probably had their greatest value as adjuncts to psychotherapy, a designation was sought that would be

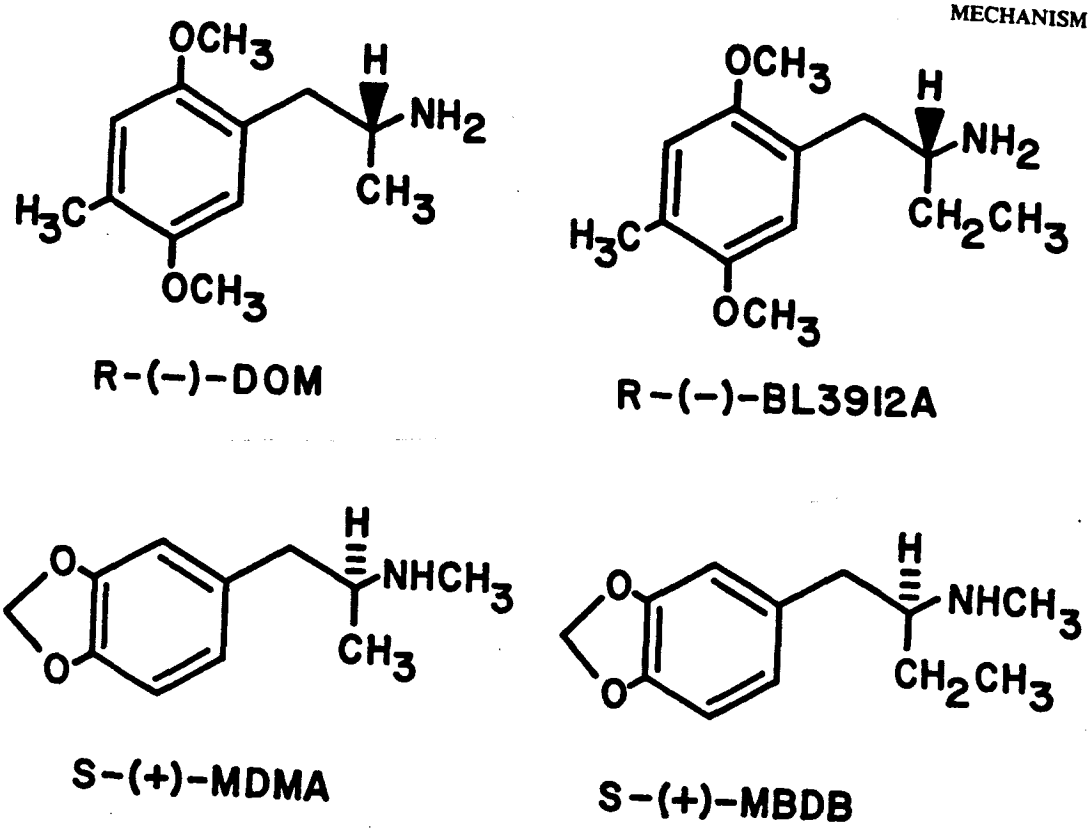

Figure 1. The more potent R-(−) enantiomers of the potent hallucinogenic amphetamine derivative DOM, and its nonhallucinogenic α-ethyl homologue BL-3912A. The more active enantiomer of MDMA has the S-(+) configuration, inverted from that of DOM, as does its α-ethyl congener MBDB. Neither of the latter compounds fit within the accepted structure-activity relationships for hallucinogenic amphetamine derivatives.

acceptable to psychiatric patients. It seemed that the effect of these drugs was to enable the therapist—or patient—to reach inside and deal with painful emotional issues that are not ordinarily accessible. Just as the word "tact" has the connotation of communicating information in a sensitive and careful way so as to avoid offense, it seemed that the Latin root of this word, *tactus*, would be appropriate as part of the term. Addition of the Greek roots *en* (within or inside) and *gen* (to produce) created the term "entactogen," having the connotation of *producing a touching within*. This designation seems to have appropriate roots, is esthetically pleasing to those who have heard it, and most importantly, appears to have no negative connotations for a potential patient.

Thus, MBDB belongs to a class of drugs that should be known as entactogens. MDMA, and even MDA, exhibit entactogenic activity, but combined perhaps with stimulant or hallucinogenic effects. This new category is justifiable and appropriate for several reasons: (1) Psychiatrists who have used MDMA as an adjunct to psychotherapy believe it to be a new type of compound; (2) Its animal and subjective human effects do not resemble those of hallucinogens; and (3) MDMA, and especially MBDB, do not fit within presently accepted structure-activity relationships for hallucinogens or psychedelics.

One additional objection has been raised to placing MDMA and related compounds into a new pharmacological class. This arises from the fact that MDA has effects in rats and dogs that seem to indicate that it resembles not only LSD, but also amphetamine (Glennon & Young 1984b) and cocaine (Glennon & Young 1984c). Because it is the dextro-isomer of MDA and MDMA that has these amphetaminelike effects in animals, and because it is the dextro-isomer of MDMA that is more active as an entactogen, it follows that perhaps this is the activity of MDMA: It is simply another amphetaminelike stimulant. Here again, MBDB has provided evidence that this is not the case, and that entactogens have a unique mechanism of action.

The stimulant effects of amphetamine and cocaine are believed to be largely due to the ability of the drugs to alter the function of neuronal pathways in the brain that utilize the neurotransmitters dopamine and norepinephrine (Moore 1978; Yokel & Wise 1975). Studies

TABLE I
RATE OF RELEASE OF ^{3}H-SEROTONIN FROM RAT WHOLE BRAIN SYNAPTOSOMES (NICHOLS ET AL. 1982)

Treatment	Drug Concentration (Molar)	K, $min^{-1} \times 10^4$, (±S.E.)
Control	–	125
R-(−)-MDA	10^{-6}	202 (15)
S-(+)-MDA	10^{-6}	242 (32)
R-(−)-MDMA	10^{-6}	173 (6)
S-(+)-MDMA	10^{-6}	284 (16)

that support this idea are too numerous to cite here. The present author's research team has examined the ability of MDA, MDMA, MBDB, and amphetamine to alter the release and uptake mechanisms for the neurotransmitters dopamine, norepinephrine and serotonin from rat brain preparations. These results will be summarized later. However, in these studies it was found that amphetamine, MDA, and MDMA all had the ability to alter the utilization of dopamine by rat brain neurons, but it was also found that MBDB had virtually no effect on neurons that utilize dopamine. Curiously, in the preliminary clinical study of MBDB, subjects also reported that MBDB produced less euphoria than did MDMA. Thus, while both MDA and MDMA have significant effects on dopamine pathways in the brain, MBDB apparently does not. This seems to set MBDB apart from stimulants, such as amphetamine and cocaine, where actions on dopamine neurons are important. It further indicates that the entactogenic effect is probably not mediated through dopaminergic pathways. Once again, MBDB served as a prototype for the entactogens, because it seems to have a pharmacological action that is less complex and easier to define.

The majority of evidence gathered to date in the present studies, as well as by other laboratories, indicates that MDMA and MBDB may exert their action by causing the release of the neurotransmitter serotonin from serotonin-containing nerve endings in the brain. There are only a few other drugs that are known to do this (e.g., fenfluramine), and they differ completely from MDMA or MBDB in their human psychopharmacology. Interestingly, drugs that block the reuptake of serotonin into nerve endings have found application as antidepressant agents. In the following discussion, a brief partial summary will be presented of the experimental results of this author's research team, which show how entactogens affect the release and reuptake of dopamine, norepinephrine, and serotonin from rat brain neuronal preparations.

SYNAPTOSOMES

The earliest biochemical pharmacology of MDMA was carried out in this author's laboratory using synaptosomes from rat brain (Nichols et al. 1982). Synaptosomes are produced by gentle mechanical disruption of brain neurons. The region where chemical transmission occurs between neurons is known as the synapse. It is here that the nerve terminal releases chemical transmitters that diffuse across the synaptic space and stimulate receptors on the postsynaptic, recipient neuronal membrane. Synaptosomes are small particles that include the neuronal terminal and its associated postsynaptic target membrane. It has most of the functions of the synapse in the intact brain, but of course has no regulation of its firing rate and has no interconnections with other neurons.

In earlier reports, it was argued that MDMA might act by releasing neurotransmitters from nerve terminals (Nichols et al. 1982; Anderson et al. 1978). This was based on the observation, noted earlier, that it is the dextro-isomer of MDMA that is more potent. Similarly, it is the dextro-isomer of amphetamine that is more effective in releasing neurotransmitter from neuronal terminals.

Briefly, a synaptosome preparation from rat brain was incubated with radioactive tritium-labeled serotonin. This preparation was then washed and supported on a filter, through which artificial cerebrospinal fluid was perfused. The synaptosomes slowly release the radioactive serotonin, without any stimulation. However, the addition of certain drugs to the bathing medium can induce rapid release of neurotransmitter. The results from those experiments are summarized in Table I and are expressed as a rate of release for the isomers of MDA and MDMA.

These data showed that both isomers of MDA released serotonin equally well and that the S-(+) isomer of MDMA is about equipotent to MDA. However, the R-(−) isomer of MDMA is less potent than its mirror image S-(+) isomer. Although there had been a suspicion that

these compounds might release neurotransmitter, this was the first time it had been shown that MDA and MDMA were potent releasing agents for serotonin.

More recently, MDA, MDMA, MBDB, the isomers of amphetamine, and the hallucinogenic drug DOM have been compared for their ability to block the reuptake of neurotransmitter into nerve terminals. In the synapse, after the nerve terminal releases its neurotransmitter, a process known as active uptake pumps the neurotransmitter back into the neuronal terminal for reuse. Some drugs, such as amphetamine, cocaine and tricyclic antidepressants, have the ability to block this reuptake process. This allows the neurotransmitter to remain in the synapse, where it continues to produce a chemical signal and stimulates postsynaptic receptors. The functional effect of this is increased transmission in the synapse.

Again, rat brain synaptosomes prepared from various brain areas were used to study this process. The synaptosomes were incubated with tritium-labeled dopamine, norepinephrine, and serotonin. The drug to be studied was also added in test experiments. Following these incubations, the synaptosomes were rapidly filtered and washed, and were then counted for radioactive neurotransmitter content. Thus, in experiments where the reuptake process was blocked, the synaptosomes would contain less radioactive neurotransmitter. As a measure of relative potency, the concentration of drug was determined that was necessary to inhibit this to half of the amount taken up by synaptosomes in the absence of any test drug (i.e., IC_{50}). Tables II, III and IV summarize the results of these studies with MDA, MDMA, MBDB, the isomers of amphetamine and the hallucinogen DOM.

Several things are evident from these data. For dopamine reuptake (Table II), (a) MBDB and DOM have no ability to block reuptake of dopamine, (b) MDMA is considerably less potent than MDA, and (c) MDA and MDMA exhibit stereoselectively. That is, their S-(+) isomers are more potent.

While it appears unlikely that inhibition of dopamine reuptake is important to the action of entactogens, it is not clear whether or not norepinephrine is involved. As seen in Table III, MDA, MDMA and MBDB are all reasonably potent inhibitors of norepinephrine reuptake. Again, it is the S-(+) isomer that is most potent. Amphetamine is a much more potent inhibitor than any other compound tested, and the hallucinogen DOM has insignificant activity.

Finally, in Table IV one can see that MDA, MDMA and MBDB are all potent inhibitors of serotonin reuptake. Amphetamine is far less active and the hallucinogen DOM again is seen not to have significant activity. Note that it is the S-(+) isomers of the entactogens that are more active.

There are some general conclusions that can be drawn from these data. The hallucinogen DOM has no effect on the reuptake process for dopamine, norepinephrine or serotonin. In clear contrast to this, MDA, MDMA and MBDB are all potent reuptake inhibitors. In addition, it is the dextro-isomer of all of the active compounds that is more potent. This correlates with the observed effects of the isomers in humans. In rats, the dextro-isomer of MDA and MDMA has an amphetaminelike action (Glennon & Young 1984a). The stimulus effect of amphetamine in rats is generally considered to be related to the ability of amphetamine to release dopamine. This finding is paralleled by the inhibition of dopamine reuptake by amphetamine in the present author's studies. However, MDMA and particularly MBDB are more than an order of magnitude less potent than amphetamine in this effect. Users' subjective descriptions of the effects of MDMA and MBDB also are quite different from those of amphetamine. Thus, the rat data do not give reliable results in ascribing an amphetaminelike action to MDMA.

The present author's research team has so far not had the opportunity to carry out further studies of the effects of entactogens on norepinephrine, but it is possible that this catecholamine neurotransmitter may be involved in their action. In any case, these entactogens are able to release serotonin and to inhibit the reuptake of serotonin and norepinephrine into nerve terminals. These are actions that are not possessed by the hallucinogenic amphetamine DOM (e.g., Whipple, Reinecke & Gage 1983). Furthermore, while amphetamine has some similar neurochemical properties, its quantitative potency in the different neurotransmitter systems varies from the entactogens. Thus, while animal studies suggest that MDMA has amphetaminelike qualities, this appears to be true only in the sense that amphetamine releases neurotransmitter and blocks reuptake, as do MDA, MDMA and MBDB.

DRUG DISCRIMINATION STUDIES

Because the present author's research team is not in a position to carry out studies in humans, it has been forced to rely on animal models. The most powerful behavioral model pharmacologists have found so far for studying psychoactive compounds is known as drug discrimination (Glennon, Rosencrans & Young 1982). Essentially, rats are trained to tell the difference between (discriminate) the effects of saline (placebo) injection from those produced by a particular drug. In the present studies, LSD was used as the training drug. Without going into the methodology in detail, suffice it to say that the procedure is very powerful and has been useful in predicting the activity of new compounds. Therefore, in rats trained to discriminate

TABLE II
IC_{50} DETERMINATIONS FOR INHIBITION OF DOPAMINE UPTAKE INTO RAT BRAIN STRIATAL SYNAPTOSOMES (STEELE, NICHOLS & YIM 1986)

Compound	S-(+) Isomer IC_{50} (μM)	R-(−) Isomer IC_{50} (μM)
Amphetamine	0.38	2.05
MDA	1.96	>5.00
MDMA	4.20	>5.00
MBDB	>5.00	>5.00
DOM	>10.00	>10.00

TABLE III
IC_{50} DETERMINATION FOR INHIBITION OF NOREPINEPHRINE UPTAKE INTO RAT BRAIN HYPOTHALAMIC SYNAPTOSOMES (STEELE, NICHOLS & YIM 1986)

Compound	S-(+) Isomer IC_{50} (μM)	R-(−) Isomer IC_{50} (μM)
Amphetamine	0.07	0.10
MDA	0.27	0.46
MDMA	0.32	0.81
MBDB	0.64	2.22
DOM	>10.00	>10.00

TABLE IV
IC_{50} DETERMINATIONS FOR INHIBITION OF SEROTONIN UPTAKE INTO RAT BRAIN HIPPOCAMPAL SYNAPTOSOMES (STEELE, NICHOLS & YIM 1986)

Compound	S-(+) Isomer IC_{50} (μM)	R-(−) Isomer IC_{50} (μM)
Amphetamine	2.55	>5.00
MDA	0.51	1.44
MDMA	0.44	1.51
MBDB	0.40	1.74
DOM	>10.00	>10.00

TABLE V
RESULTS OF DRUG DISCRIMINATION STUDIES IN RATS TRAINED TO DISCRIMINATE LSD TARTRATE (0.08 MG/KG) FROM SALINE (NICHOLS ET AL. 1986)

Treatment	ED_{50} (mg/kg)	Animals Selecting LSD Lever (%)*	Dose (mg/kg)
Saline	–	–	–
LSD	0.011	–	–
(±)-MDA	0.970	–	–
(−)-MDA	0.630	–	–
(+)-MDA	–	38	1.29
(±)-MDMA	–	38	1.84
(−)-MDMA	–	50	3.44
(+)-MDMA	–	50	1.72
(±)-MBDB	–	14	1.95
(−)-MBDB	–	38	2.92
(+)-MBDB	–	50	2.56

*This value is reported when no LSD generalization occurred. It represents the highest percentage of rats selecting the LSD lever and the dose at which this response level occurred. Each drug was tested at from four to 11 different dose levels, and in five to 30 animals at each dose.

between saline and LSD tartrate (0.08 mg/kg administered intraperitoneally), it can be determined whether a drug produces an effect similar to LSD (i.e., the drug substitutes or generalization occurs) or if its effects are dissimilar. If generalization is obtained, then the drug might be expected to have LSD-like actions in humans. In Table V the results of studies are summarized where the isomers of MDA, MDMA and MBDB were compared in a colony of rats trained in this way.

As seen in Table V, only MDA produced an LSD-like stimulus. Taken together with the work that has been reported by Glennon and his colleagues (who employed the same methods, but used rats trained to discriminate DOM as the hallucinogen stimulus), these results show that MDMA and MBDB do not have hallucinogenlike effects in rats. Although it may seem curious that rats are needed to reveal something that has already been reported by humans, there is a reluctance by regulatory agencies to believe anecdotal human data. As surprising as it seems, it may take a preponderance of negative data from studies in a variety of animal models before there is official acceptance of the premise that MDMA is not a hallucinogen.

CONCLUSIONS

In summary, this article has presented evidence based on the known structure-activity relationships of psychoactive compounds and studies of several biochemical parameters as well as behavioral data in rats that show that MDMA and particularly MBDB do not fit into the pharmacological classification of hallucinogen or psychedelic. Furthermore, these compounds differ sufficiently in their biochemical pharmacology profiles to distinguish them from amphetamine. Therefore, if MDMA and MBDB are not hallucinogens and are not simply stimulants, what are they? Based on their unique human psychopharmacology, it is believed that they represent a new drug category. There is no other known class of psychoactive agents that produces effects similar to these compounds. Thus, the present author's research team has proposed that this new pharmacological class be designated entactogens.

REFERENCES

Anderson, G.M., III; Braun, G.; Braun, U.; Nichols, D.E. & Shulgin, A.T. 1978. Absolute configuration and psychotomimetic activity. In: Barnett, G.; Trsic, M. & Willette, R. (Eds.). *QUASAR: Quantitative Structure Activity Relationships of Analgesics, Narcotic Antagonists, and Hallucinogens*. NIDA Research Monograph 22. Rockville, Maryland: NIDA.

Glennon, R.A.; Rosecrans, J.A. & Young, R. 1982. The use of the drug discrimination paradigm for studying hallucinogenic agents. A review. In: Colpaert, F.C. & Stangen, J.L. (Eds.). *Drug Discrimination: Applications in CNS Pharmacology*. Amsterdam: Elsevier.

Glennon, R.A. & Young, R.Y. 1984a. Further investigation of the discriminative stimulus properties of MDA. *Pharmacology, Biochemistry and Behavior* Vol. 20: 501-505.

Glennon, R.A. & Young, R.Y. 1984b. MDA: A psychoactive agent with dual stimulus effects. *Life Sciences* Vol. 34: 379-383.

Glennon, R.A. & Young, R. 1984c. MDA: An agent that produces stimulus effects similar to those of 3,4-DMA, LSD and cocaine. *European Journal of Pharmacology* Vol. 99: 249-250.

Glennon, R.A.; Young, R. & Rosecrans, J. 1983. Antagonism of the effects of the hallucinogen DOM and the purported 5-HT agonist quipazine by 5-HT_2 antagonists. *European Journal of Pharmacology* Vol. 91: 189-196.

Glennon, R.A.; Young, R.; Rosecrans, J.A. & Anderson, G.M., III. 1982. Discriminative stimulus properties of MDA and related agents. *Biological Psychiatry* Vol. 17: 807-814.

Lyon, R.A.; Glennon, R.A. & Titeler, M. 1986. 3,4-Methylenedioxymethamphetamine (MDMA): Stereoselective interactions at 5-HT_1 and 5-HT_2 receptors. *Psychopharmacology* Vol. 88: 525-526.

Moore, K.E. 1978. Amphetamines: Biochemical and behavioral actions in animals. In: Iversen, L.L.; Iversen, S.D. & Snyder, S.H. (Eds.). *Handbook of Psychopharmacology*. Vol. 11. New York: Plenum.

Naranjo, C.; Shulgin, A.T. & Sargent, T. 1967. Evaluation of 3,4-methylenedioxyamphetamine (MDA) as an adjunct of psychotherapy. *Medicina et Pharmacologia Experimentalis* Vol. 17: 359-364.

Nichols, D.E. & Glennon, R.A. 1984. Medicinal chemistry and structure-activity relationships of hallucinogens. In: Jacobs, B.L. (Ed.). *Hallucinogens: Neurochemical, Behavioral, and Clinical Perspectives*. New York: Raven Press.

Nichols, D.E.; Hoffman, A.J.; Oberlender, R.A.; Jacob, P., III & Shulgin, A.T. 1986. Derivatives of 1-(1,3-benzodioxol-5-yl)-2-butanamine. Representatives of a novel therapeutic class. *Journal of Medicinal Chemistry* Vol. 29: 2009-2015.

Nichols, D.E.; Lloyd, D.H.; Hoffman, A.J.; Nichols, M.B. & Yim, G.K.W. 1982. Effects of certain hallucinogenic amphetamine analogues on the release of [^{3}H]serotonin from rat brain synaptosomes. *Journal of Medicinal Chemistry* Vol. 25: 530-534.

Nozaki, M.; Vaupel, D.B. & Martin, W.R. 1977. A pharmacologic comparison of 3,4-methylenedioxyamphetamine and LSD in the chronic spinal dog. *European Journal of Pharmacology* Vol. 46: 339-349.

Shulgin, A.T. 1978. Psychotomimetic drugs: Structure-activity relationships. In: Iversen, L.L.; Iversen, S.D. & Snyder, S.H. (Eds.). *Handbook of Psychopharmacology*. Vol. 11. New York: Plenum.

Shulgin, A.T. 1973. Stereospecific requirements for hallucinogenesis. *Journal of Pharmacy and Pharmacology* Vol. 25: 271-272.

Shulgin, A.T. 1963. Psychotomimetic agents related to mescaline. *Experientia* Vol. 19: 127-128.

Standridge, R.T.; Howell, H.G.; Gylys, J.A.; Partyka, R.A. & Shulgin, A.T. 1976. Phenylalkylamines with potential psychotherapeutic utility. 1. 2-Amino-1-(2,5-dimethoxy-4-methylphenyl)butane. *Journal of Medicinal Chemistry* Vol. 19: 1400-1404.

Steele, T.D.; Nichols, D.E. & Yim, G.K.W. 1986. Stereochemical effects of 3,4-methylenedioxymethamphetamine (MDMA) and related compounds on inhibition of ^{3}H-monoamine uptake into synaptosomes from different regions of rat brain. *Biochemical Pharmacology* (submitted for publication).

Thiessen, P.N. & Cook, D.A. 1973. The properties of 3,4-methylenedioxyamphetamine (MDA). II. Studies of acute toxicity in the mouse and protection by various agents. *Clinical Toxicology* Vol. 6: 193-199.

Whipple, M.R.; Reinecke, M.G. & Gage, F.H. 1983. Inhibition of synaptosomal neurotransmitter uptake by hallucinogens. *Journal of Neurochemistry* Vol. 40: 1185-1188.

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* Vol. 68: 159-162.

Yokel, R.A. & Wise, R.A. 1975. Increased lever pressing for amphetamine after pimozide in rats: Implications for a dopamine theory of reward. *Science* Vol. 187: 547-549.