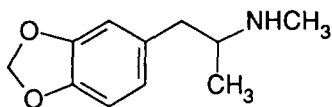


Structure-Activity Relationships of MDMA-Like Substances

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INTRODUCTION

There is virtually no one who is involved in drug abuse research, or who studies the properties of recreationally used drugs, that is not by now familiar with 3,4-methylenedioxymethamphetamine (MDMA) (figure 1). Over the past 4 years this substance, usually referred to in the popular press as “Ecstasy,” has received widespread media attention. This chapter will relate recent findings with respect to the potential dangers attendant on the use of MDMA and explore its pharmacological properties.



MDMA (1)

FIGURE 1. *MDMA*

As the title implies, MDMA has pharmacological properties that set it apart from other classes of drugs. This is one of the most intriguing aspects of MDMA, largely overlooked as researchers examined the potential risks to health of MDMA use. Basic questions of how drugs work and why some are pleasurable and some are not are fundamental to our understanding of why humans use drugs. Although much of the popularity of MDMA can no doubt be attributed to curiosity following media attention, the drug itself must have some rewarding qualities.

MDMA typifies a central problem with the substituted amphetamine-type substances: The fact that we know so little about any of these kinds of drugs. What does MDMA actually do? What are the psychopharmacological properties that make it attractive for recreational use? Is it “just another hallucinogenic amphetamine,” as some have asserted? In the following

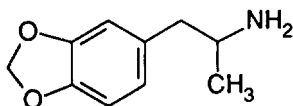
discussion, an attempt will be made to address some of these issues, and to put the questions into a broader perspective.

MDMA was patented in 1914 by a German pharmaceutical firm and evaluated as an appetite suppressant (Shulgin 1986). In that sense, MDMA is not a “designer drug.” Its rediscovery in the late 1970s probably had little to do with the fact that it was, technically speaking, a legal drug. There were a variety of legal psychoactive drugs, many of which could probably have been synthesized and marketed with greater economic profit than MDMA, a substance with unremarkable quantitative potency, being only two to three times more active on a weight basis than mescaline (Shulgin and Nichols 1978). Nonetheless, no other substituted amphetamines with the popularity of MDMA have appeared. The explanation seems to be that MDMA has psychopharmacological properties that are deemed especially rewarding to the user.

MDMA is believed to have unique psychoactive properties that clearly distinguish it from hallucinogenic or psychostimulant phenethylamines. Not only have MDMA users consistently reported this distinctiveness, but subsequent studies of MDMA and similar compounds, in many laboratories, have shown that they do not fit within the structure-activity relationships that presently are understood to define the hallucinogenic amphetamines.

STRUCTURAL FEATURES OF MDMA

One of the structural features of MDMA that is somewhat unusual is the fact that it is 3,4-disubstituted. Both 3,4-methylenedioxyamphetamine (MDA) (figure 2) and MDMA possess the 3,4-methylenedioxy function, and there apparently are no other active compounds known that fall within the



MDA (2)

FIGURE 2. *MDA*

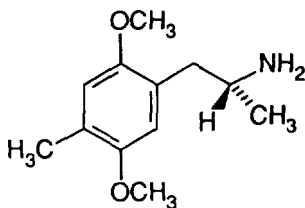
substituted amphetamine class and have substituents only in the 3 and 4 positions. The largest group of substituted amphetamines with significant hallucinogenic potency possess either 3,4,5- or 2,4,5- trisubstitution patterns. The parent compound MDA, although classified as a hallucinogenic amphetamine and available on the illicit market for about 20 years, had gained a reputation as the “love drug” (Weil 1976). It had been recognized for many years by both recreational drug users and clinicians (Turek et al. 1974) that

MDA had unique psychoactive properties that were different from hallucinogens such as LSD or mescaline. While MDA in high doses appears to be hallucinogenic or psychotomimetic, it seems not to have been used for this effect, 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 talk to other people (Jackson and Reed 1970). MDA is also the only substituted amphetamine that received serious clinical study as an adjunct to psychotherapy (Yensen et al. 1976).

A second 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- or 2,4,5-substituted phenethylamine derivatives, N-methylation decreases hallucinogenic potency by up to an order of magnitude (Shulgin 1978). When MDA is ingested, the hallucinogenic effects are long lasting, typically 10 to 12 hours, similar to the duration of LSD or mescaline. By contrast, MDMA has a much shorter action, with perhaps a 3- to 5-hour duration of effects. There is no evidence that typical doses of MDMA lead to hallucinogenic effects in a significant proportion of users, although in high doses hallucinogenic effects have been reported (Siegel 1986). 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.

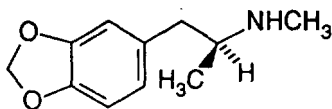
A third important difference between MDMA and the hallucinogenic amphetamines is the reversal of stereochemistry that occurs in MDMA. In every substituted hallucinogenic amphetamine that has been studied, the isomer with the *R* absolute configuration in the side chain is more potent in animal models, in a variety of *in vivo* assays, and in man (figure 3). The two isomers differ in potency by a factor of 3 to 10, depending on the assay system (Nichols and Glennon 1984). By contrast, the *S* isomer of MDMA is more potent (figure 4). This was first reported in experiments with rabbits and in clinical studies (Anderson et al. 1978), and it has recently been confirmed in other animal models (Oberlander and Nichols 1988; Schechter 1987).

It is difficult to trivialize the significance of this argument, since the stereospecificity 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 to accommodate a side chain stereochemistry reversed from that for phenylisopropylamines with other aromatic substituents.



R-(-)-DOM

FIGURE 3. *The more active R-(-)-enantiomer of the hallucinogenic amphetamine DOM*



S-(+)-MDMA

FIGURE 4. *The more active S-(+)-enantiomer of MDMA*

Several studies have now clearly shown that the *R* enantiomer of MDA has the hallucinogenic effects of the racemate, while the *S* enantiomer possesses more potent MDMA-like properties than the *R* in animals models (Anderson et al. 1978; Shulgin 1978; Glennon and Young 1984a; Nichols et al. 1982; Nichols et al. 1986; Oberlender and Nichols 1988). Further, although (+)-MDA appears similar to amphetamine in the drug discrimination assay in rats (Glennon and Young 1984a), it is not generally realized that the effects of (+)-MDA in humans qualitatively resemble those of MDMA, rather than those of amphetamine (Shulgin, personal communication, 1985). This is a unique situation. Both enantiomers of MDA are active, having nearly equal quantitative potencies, but differing in qualitative effect. N-methylation of the racemic material dramatically and selectively attenuates the hallucinogenic effects of the *R* enantiomer, while essentially leaving intact the properties of the *S* enantiomer.

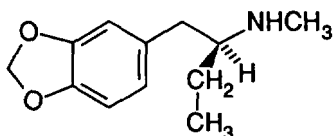
In earlier proposals (Anderson et al. 1978), based on this stereoselectivity for the *S* enantiomer of MDMA, it was suggested that, rather than having a direct effect at serotonin receptors, perhaps MDMA was a neurotransmitter-releasing agent, acting in a fashion similar to amphetamine, for which the *S* enantiomer is also more active than the *R* enantiomer. A subsequent study

in our laboratory indicated that the *S* isomers of MDA and MDMA were indeed potent releasers of [^3H]serotonin from prelabeled rat brain synaptosomes (Nichols et al. 1982). Recently, it was reported that MDA and MDMA were potent releasers of serotonin from superfused hippocampal slices prelabeled with [^3H]serotonin (Johnson et al. 1986). In all studies to date, whether of release of monoamines from synaptosomes or brain slices, or of the inhibiting of monoamine reuptake into synaptosomes (Steele et al. 1987), the *S* enantiomer of MDMA is either equipotent to the *R* isomer or more potent.

THE ENTACTOGENS

As a consequence of these and other studies that have indicated that MDMA has a pharmacology different from the hallucinogenic amphetamines, and in view of the reports by certain psychiatrists (Greer and Tolbert 1986; Wolfson 1986) that MDMA could facilitate the process of psychotherapy, it was hypothesized that MDMA and related compounds represent a new pharmacological class, with as yet unexplored potential as psychiatric drugs (Nichols 1986; Nichols et al. 1986). This class of drugs has been called entactogens. Recently, efforts have been directed toward understanding the mechanism of action of MDMA and related compounds and testing the hypothesis that entactogens are a novel pharmacological class, distinct both from hallucinogenic agents and from central stimulants such as amphetamine or cocaine.

Important support for this hypothesis came from the discovery that the alpha-ethyl homolog of MDMA, MBDB (figure 5) possessed MDMA-like

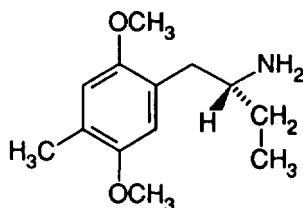


S-(+)-MBDB (3)

FIGURE 5. The *S*-(+)-enantiomer of the alpha-ethyl homologue of MDMA, MBDB

properties in man and in the drug-discrimination paradigm in rats (Nichols et al. 1986; Oberlender and Nichols 1988). It was known that homologation of the alpha-methyl of the hallucinogenic amphetamines completely abolished hallucinogenic activity (Standridge et al. 1976). For example, the alpha-ethyl homolog of *R*-DOM, BL-3912A (figure 6) was evaluated by a major pharmaceutical firm and found to lack hallucinogenic activity at doses more than a hundredfold higher than those effective for DOM (Winter 1980). This additional feature of the entactogens, that the alpha-ethyl

homologs retained activity, was a final and most powerful argument that MDMA, and certainly MBDB, could not fit within the well-established structure-activity relationships of the hallucinogenic amphetamines.



R-(-)-BL3912A (4)

FIGURE 6. *The nonhallucinogenic alpha-ethyl homologue of DOM, BL-3912A*

STUDIES OF STRUCTURE-ACTIVITY RELATIONSHIPS

EEG Studies

Recently, Dr. W. Dimpfel has used quantitative radioelectroencephalography in the rat to characterize the electroencephalograph (BEG) "fingerprint" of hallucinogenic amphetamines, MDMA, and MBDB. In this technique, four bipolar stainless steel electrodes are chronically implanted in each of four brain regions in rats: the frontal cortex, the hippocampus, the striatum, and the reticular formation (Dimpfel et al. 1986). The rats are freely moving; 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 4 seconds, segmented into six frequency bands, and averaged on each channel over timeblocks of 15 minutes.

Using this method, a variety of hallucinogenic and nonhallucinogenic compounds were examined. As previously reported (Spüler and Nichols 1988), hallucinogens produce a marked increase of power in the α_1 frequency (7.0 to 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 (Dimpfel et al. 1988). With 5-HT_{1A} agonists, however, 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 by six frequency bands per electrode) that resembled that produced by the hallucinogenic amphetamines DOM, DOB, DOI, or LSD. These data are consistent with the results obtained in other models and further support the hypothesis that MDMA and MBDB are not hallucinogenic phenethylamines.

Thus, for this class of psychoactive agent, preliminary structure-activity relationships are being formulated. Currently, four structural features 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 has only a minor effect on entactogens.

Drug Discrimination Studies

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. A significant problem with the hypothesis remained: showing that entactogens differed from another structurally related class, the central nervous system (CNS) stimulants. Several studies have characterized MDMA as an amphetamine-like or cocaine-like agent, based on its stimulus properties or its self-administration in primates (Beardsley et al. 1986; Lamb and Griffiths 1987; Evans and Johanson 1986; Kamien et al. 1986). It is well known that both amphetamine and cocaine have powerful effects on dopamine pathways in the brain, and it seems likely that drugs that release dopamine, or stimulate dopamine receptors, have reinforcing properties that lead to self-administration and dependence liability (Wise and Bozarth 1987).

It could not be anticipated 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 (Steele et al. 1987) or on release of dopamine from caudate

slices (Johnson et al. 1986). In subsequent drug discrimination experiments in rats, the dopaminergic properties of MDMA were evident, while MBDB seemed to have a pharmacologically “cleaner” discriminative cue.

To characterize further the behavioral pharmacology of MDMA and MBDB, extensive drug discrimination studies were carried out using rats trained to discriminate saline from LSD, saline from (+)-amphetamine, saline from (±)-MDMA, and saline from (+)-MBDB. Table 1 summarizes the results of those experiments. As is the case with hallucinogens, the drug discrimination paradigm should not be considered, in strict terms, an animal model for entactogen activity. Yet, data from these experiments can provide a good initial behavioral evaluation of the qualitative and quantitative effects of a variety of compounds of interest.

It is clear from these results that, in MDMA- or MBDB-trained rats, complete generalization of the training cue to the typical hallucinogenic drugs LSD, DOM, and mescaline does not occur. Furthermore, transfer of the training stimulus does not occur to MDMA or MBDB in animals trained to discriminate LSD from saline (Nichols et al. 1986). Although MDMA has been shown to substitute for mescaline (Callahan and Appel 1987). (+)-MBDB-trained rats did not recognize the mescaline cue as similar to the training drug. These results are consistent with the conclusion that MDMA and MBDB are not hallucinogenic, as discussed earlier.

These data clearly illustrate the enantioselectivity of the (+)-isomers of MDA, MDMA, and MBDB in producing an MDMA-like stimulus and underscore the fact that *in vitro* studies of the biochemical pharmacology of these substances should reveal similar selectivity, once the primary pharmacological process underlying the interoceptive cue is identified. The data also indicate that (+)-MDA is the most potent of all the drugs tested in MDMA- or in (+)-MBDB-trained animals. The fact that (+)-MDA does not substitute in amphetamine-trained animals in our studies supports the argument that the pharmacology of this enantiomer of MDA is MDMA-like and is not like amphetamine.

Although amphetamine substitutes for MDMA in our studies, this occurs only at doses that disrupt a significant number of animals. Furthermore, the large ED₅₀ 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 man, or in animal assays of its activity as a CNS stimulant, amphetamine is perhaps 10 times more potent than MDA or MDMA. Thus, its large ED₅₀ 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.” Although some investigators have reported stimulus transfer with MDMA in animals trained to discriminate amphetamine from saline, in our paradigm no substitution occurred.

TABLE 1. *Results of drug discrimination transfer tests in LSD, (+)-amphetamine, (±)-MDMA, or (+)-MBDB-trained rats (ED₅₀ expressed in micromoles per kilogram of body weight)*

Substitution Drug	LSD	Training Drug AMP	Drug MDMA	(+)-MBDB
LSD	0.025	NS	PS ¹	PS ²
DOM	0.61	NS	NS	NS
(+)-AMP	NS	1.68	4.22	NS
(+)-MDA	NS	NS	1.63	1.43
(-)-MDA	2.94	NS	2.27	3.09
(+)-MDMA	NS	NS	1.92	1.67
(-)-MDMA	NS	NS	5.03	3.09
(+)-MBDB	NS	NS	3.67	3.28
(-)-MBDB	NS	NS	6.71	6.51
Cocaine	NT	20.0	13.9	PS ³
Mescaline	33	NS ^b	NT	NS
Fenfluramine	PS ⁴	NS	NT	2.01

KEY: NS=no substitution occurred; PS=partial substitution; NT=not tested.

NOTE: Training doses: LSD tartrate 0.186 $\mu\text{mol/kg}$; (+)-amphetamine sulfate 5.43 $\mu\text{mol/kg}$; racemic MDMA.HCl 7.63 $\mu\text{mol/kg}$; and (+)-MBDB.HCl 7.19 $\mu\text{mol/kg}$.
¹78% at 0.372 $\mu\text{mol/kg}$; ²57% at 0.186 $\mu\text{mol/kg}$; ³63% at 29.42 $\mu\text{mol/kg}$; and ⁴71% at 4.68 $\mu\text{mol/kg}$.

SOURCES: Stolerman and D'Mello 1981; Schechler and Rosecrans 1973.

Differences in experimental design or in numbers of animals and doses tested may account for this discrepancy. In our experiments, symmetrical transfer did not occur between MDMA and amphetamine.

These results show that the MDMA cue is 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. This partial amphetamine-like action is believed to

be reflective of the effect that MDMA has on dopaminergic pathways (Johnson et al. 1986; Steele et al. 1987). Other workers have reached similar conclusions (Gold and Koob 1988).

Similarly, self-administration of MDMA in monkeys trained to self-administer amphetamine (Kamien et al. 1986) or in monkeys or baboons trained to self-administer cocaine (Beardsley et al. 1986; Lamb and Griffiths 1987) probably reflects a dopaminergic component to the pharmacology of MDMA. This would be consistent with current theories of dopamine involvement in the mechanism of action of drugs with dependence liability (Wise and Bozarth 1987).

In vitro studies have also shown that the alpha-ethyl congener MBDB lacks significant effects on dopamine systems in the brain. The drug discrimination data support this idea, and amphetamine does not substitute in (+)-MBDB-trained rats. Furthermore, while cocaine fully substitutes in MDMA-trained rats, it produces partial substitution in (+)-MBDB-trained rats. This is further evidence of the decreased effect of MBDB on catecholaminergic systems. If the data have been interpreted correctly, this might suggest that MBDB would not be self-administered in animal models of dependence behavior, and, hence, might have low abuse potential. It has been found, however, that (+)-MBDB produces serotonin neurotoxicity in rats, although MBDB is somewhat less toxic than MDMA (Johnson and Nichols, unpublished).

To summarize the data in table 1, neither MDMA nor MBDB has hallucinogen-like discriminative stimulus properties. Symmetrical transfer of the MDMA and MBDB stimulus indicates that their primary discriminative stimulus effects are very similar. For both MDMA and MBDB, there is enantioselectivity for the *S* isomer, with about a twofold eudismic ratio. Finally, the substitution of (+)-amphetamine and cocaine in MDMA-trained rats may indicate that MDMA has some psychostimulant-like properties, while MBDB seems to lack this activity.

Effect of the Side Chain Alpha-Ethyl

It seemed likely that an alpha-ethyl moiety would attenuate the ability of other phenethylamines to interact with dopaminergic systems. To test this hypothesis, the alpha-ethyl homolog of methamphetamine was synthesized. This compound (figure 7) was also tested in the drug discrimination paradigm in (+)-amphetamine trained rats, and compared with (+)-methamphetamine. While (+)-methamphetamine was found to have an ED_{50} of 1.90 micromoles per kilogram ($\mu\text{mol/kg}$), the racemic alpha-ethyl homolog only produced full substitution at high doses, and had an ED_{50} of 19.62 $\mu\text{mol/kg}$, making it approximately one-tenth the potency of (+)-methamphetamine. This confirmed our speculation, and illustrated that the alpha-ethyl group

was effective in reducing the effect of phenethylamines on catecholamine pathways.

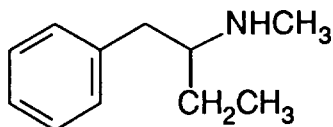


FIGURE 7. *The alpha-ethyl homologue of methamphetamine*

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.

Table 2 is a summary of drug discrimination testing data for drugs that completely substitute in rats trained to discriminate saline from (+)-MBDB-HCl (1.75 mg/kg; 7.19 μ mol/kg). These data are arranged in order of decreasing relative potency.

It is clear that the (+)-isomers of MDA and MDMA are the most potent in producing an MBDB-like cue. Furthermore, the stimulus produced by (+)-MDA is probably unlike that produced by amphetamine, based on the data presented in the earlier table. Thus, if the psychopharmacology of (+)-MDA is like that of MDMA, then N-methylation has little effect on the entactogenic properties of the molecule, but serves primarily to attenuate the hallucinogenic activity of (-)-MDA. Nevertheless, (-)-MDA also substitutes, and 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 illustrates why detailed studies of the mechanism of action of psychoactive compounds should be done on the pure optical isomers.

But what is the effect of MBDB or MDMA? We have been attempting to define this through the use of drug discrimination assays, with rats trained to a variety of drugs. Through the use of appropriate agonists and antagonists, we may be able to define the pharmacology of MBDB. Although there are some exceptions (e.g., fenfluramine), most of the substituted phenethylamines described in the literature can be categorized as hallucinogens or as stimulants. The psychopharmacology of MDMA perhaps represents a third category, and it is possible that other phenethylamine and amphetamine derivatives may possess similar pharmacology,

TABLE 2. *Compounds that completely substitute for (+)-MBDB in drug discrimination tests in rats*

Test Drug	ED ₅₀ (μ mol/kg)	95% Confidence Interval
S-(+)-MDA	1.43	0.9 - 2.29
S-(+)-MDMA	1.67	0.98 - 2.86
Fenfluramine	2.01	1.30 - 3.09
($\pm$)-MDA	2.09	1.36 - 3.21
($\pm$)-MBDB	2.92	2.17 - 3.92
R-(-)-MDMA	3.09	1.80 - 5.32
R-(-)-MDA	3.09	1.88 - 5.07
S-(+)-MBDB	3.28	2.15 - 5.01
($\pm$)-MDMA	3.35	2.35 - 4.77
R-(-)-MBDB	6.51	4.54 - 9.34

In view of the apparent pleasurable effects of MDMA, it becomes of considerable interest to understand the mechanism of action of substances with a similar effect. Major efforts have been directed toward the study of agents that have an effect on serotonin pathways, since that is the neurotransmitter system that seems most implicated in the mechanism of action of MDMA. This hypothesis is further reinforced by the observation that MDMA substitutes for fenfluramine (Schechter 1986), and fenfluramine substitutes for MBDB (Oberlender and Nichols, unpublished). The substitution data for (+)-amphetamine and cocaine in (+)-MBDB-trained rats are also similar to the data for substitution of these agents in fenfluramine-trained rats (White and Appel 1981).

However, the specific serotonin uptake inhibitor fluoxetine failed to produce an MBDB-like cue and failed to block the stimulus effects of MBDB when it was given prior to a training dose of MBDB. Table 3 summarizes results of fluoxetine testing in MBDB-trained rats. In other exploratory studies, pretreatment of MDMA-trained rats with either methysergide or ketanserin failed to block completely the MDMA-discriminative stimulus.

Based on the modest ability of the (+)-isomers of MDMA and MBDB to inhibit the reuptake of norepinephrine (NE) into hypothalamic synaptosomes (Steele et al. 1987), 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 NE uptake inhibitor (-)-tomoxetine was tested for stimulus transfer in doses up to 10 mg/kg in MDMA-trained rats. At 5 mg/kg, 67 percent of the animals responded on the drug lever. However, pretreatment with tomoxetine in six rats trained to discriminate MDMA from saline had no effect on the discrimination of a subsequent dose of MDMA.

TABLE 3. *Results of tests for fluoxetine substitution in (+)-MBDB.HCl-trained (1.75 mg/kg) rats*

Dose of Fluoxetine	N	Percentage Selecting Drug Lever
7.23 μ mol/kg	8	38%
14.46 μ mol/kg	8	50%
29.92 μ mol/kg	7	43%

At the present time, a variety of other pharmacological agents are being tested for their ability either to antagonize or to potentiate the effect of MDMA in these animals. There is hope that appropriate pharmacological manipulations will eventually be found that will give useful information about the mechanism of action for entactogens.

ANALYSIS OF STRUCTURE-ACTIVITY RELATIONSHIPS

Medicinal chemists have a distinct advantage in pursuing mechanism-of-action studies because it is possible to synthesize a series of structurally related congeners and measure their biological activity. A correlation between activity and particular structural features not only helps to identify the pharmacophore, or active moiety imbedded within the molecule, but also may establish critical requirements or complementarity for the biological target or receptor for the particular drug class.

When a particular behavioral pharmacology is associated with a specific biochemical action within a series of congeners, it is likely that the biochemistry is a functional component of the observed behavioral activity. This is not necessarily the case if only one or a few molecules are available for study; they may well possess ancillary biochemical pharmacology that is

unrelated to the behavioral phenomenon being observed. However, the larger the series of structurally diverse molecules in which the two activities are associated, the stronger the basis for believing that a cause-effect relationship exists.

In designing studies of the structure-activity relationships of MDMA and related substances, there are at least three areas for structural modification. First, the nature of the amine substituents can be varied: other N-alkyls can be studied, or the nitrogen can be incorporated into a ring system. A second point for structural modification is the side chain. As already demonstrated, the alpha-methyl can be extended to an alpha-ethyl. Other modifications of the side chain would include incorporation into a variety of ring systems, or α,α -dialkylation. Finally, the nature and location of the ring substituents can be modified.

N-Alkylation

A number of investigators have examined the N-ethyl congener of MDMA, MDE (or MDEA), which has also gained popularity on the illicit market. Braun et al. (1980) have reported that, of the N-substituted MDA derivatives that were studied for analgesic action and human psychopharmacology, only the N-methyl, N-ethyl, and N-hydroxy compounds were active. The latter compound, the N-hydroxy, in all probability serves merely as a prodrug for MDA, being metabolically reduced to the primary amine, as has been observed for para-chloramphetamine (PCA) (Fuller et al. 1974). Since the range of modification of N-substitution seems so limited, it appears unlikely that studies of N-substituted MDA analogs will offer significant insight into mechanism of action. However, different N-alkyl groups may affect regional brain distribution and pharmacokinetic properties. For example, Boja and Schechter (1987) have found that the N-ethyl analog MDE has a much shorter biological half-life than does MDMA.

Ring Substituents

Little is presently known about requirements for particular aromatic ring substituents enabling a compound to possess MDMA-like activity. The 3,4-ethylidenedioxy and 3,4-isopropylidenedioxy compounds (figures 8 and 9) have been examined for ability to substitute in LSD- 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 4. Addition of steric bulk to the dioxole ring reduces CNS activity, whether defined as LSD-like or MDMA-like. Fenfluramine also produces a cue that is similar to both MDMA and MBDB, in that complete substitution occurs and does so at a relatively low dose of fenfluramine. This would seem to imply that the dioxole ring is

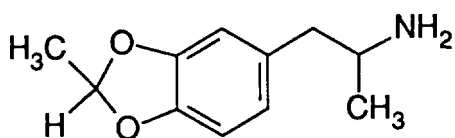


FIGURE 8. *The dioxole-ring methylated homologue of MDA, EDA*

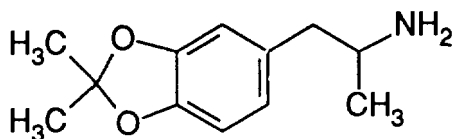


FIGURE 9. *The dioxole-ring dimethylated homologue of MDA, IDA*

not essential, and many workers have drawn comparisons between the neurotoxicity of fenfluramine and that of MDMA. However, the psychopharmacology of fenfluramine is quite different from that of MDMA.

TABLE 4. *ED₅₀ values for substitution in LSD-trained or MDMA-trained rats, in the drug discrimination paradigm*

Compound	LSD ED ₅₀ (mg/kg)	MDMA ED ₅₀ (mg/kg)
MDA (figure 2)	0.97	0.88
EDA (figure 8)	3.07	1.86
IDA (figure 9)	7.12	5.21

NOTE: LSD tartrate=0.08 mg/kg, IP; (±)-MDMA.HCl=1.75 mg/kg, IP.

While MDMA produces CNS stimulation and euphoria, fenfluramine is more of a sedative and dysphoric. A detailed comparison of the pharmacology of fenfluramine and MDMA may be necessary to understand exactly how MDMA works.

Another study underway has begun to examine the effect of paramethoxy-amphetamine (PMA) in MDMA-trained rats. After testing a few doses, it appears that full substitution may occur and that the *S* enantiomer of PMA

is more potent. This result would also 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 vitro (Tseng et al. 1978) and in vivo (Tseng et al. 1976; Nichols et al. 1982). PMA is also a potent releaser of NE in peripheral tissues (Cheng et al. 1974) but the blockade of its behavioral effects by chlorimipramine (Tseng et al. 1978) 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 (Cimbura 1974), and its use subsequently declined.

One might also speculate that PCA would have an effect similar to MDMA. Indeed, the early clinical data for PCA suggested that it possessed antidepressant activity (Verster and Van Praag 1970). This would suggest that the human psychopharmacology of PCA may well be closer to that of MDMA than fenfluramine, but it is unlikely that clinical studies can be carried out to study this.

Side-Chain Modifications

A variety of side-chain modified analogs of MDMA and MBDB have begun to be examined. Very early studies were of the α,α -dimethyl analog, 3,4-methylenedioxyphentermine (figure 8a) and its N-methyl derivative (figure 10). This latter compound proved to lack MDMA-like activity (Shulgin, unpublished). Interestingly, this compound also lacked the ability to stimulate the release of [3 H]serotonin from prelabeled rat brain synaptosomes (Nichols et al. 1982).

Recently the tetralin and indan analogs of MDA have been examined (figures 11 to 14). It was previously shown that when hallucinogenic amphetamine derivatives were incorporated into similar structures, the hallucinogen-like activity in animal models was lost (Nichols et al. 1974). Thus, one might anticipate that a similar strategy with MDMA would 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 5, one positional isomer is clearly preferred for MDMA-like activity. Furthermore, the indan derivative, figure 12, has a potency at least comparable to that of MDMA. This series has begun to define some of the conformational preferences of the receptor or target sites with which MDMA interacts, at least in producing its discriminative cue.

NON NEUROTOXIC ENTACTOGENS?

Although the problem of MDMA abuse has generated great interest because of MDMA's potential neurotoxicity, it is possible that nonneurotoxic entactogens can be developed. As in most areas of technology, this is a

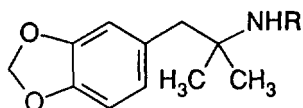


FIGURE 10. *The α , α -dimethyl homologues of MDA(a) and MDMA(b)*

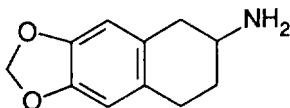


FIGURE 11. *Nonneurotoxic tetralin analogue of MDMA*

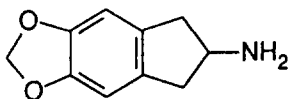


FIGURE 12. *Nonneurotoxic indan analogue of MDMA*

two-edged sword. A major concern might be that a nonneurotoxic entactogen could become popular as a recreational drug. A major deterrent to widespread use of MDMA should be the consideration by potential MDMA users that there is the possibility of neurotoxicity with unknown consequences, perhaps delayed for years before the consequences become manifest. On the other hand, researchers must give serious attention to the fact that any possible clinical utility for MDMA-like substances cannot be explored until the issue of neurotoxicity is resolved. Hence, a nonneurotoxic MDMA congener would allow clinical testing of the assertion that these compounds are useful adjuncts to psychotherapy.

Undoubtedly, nonneurotoxic entactogens can and will be discovered. Sufficient evidence already exists to support this hypothesis. We know, for example, from the work of Schechter (1986) that the discriminative stimulus properties of MDMA are largely dissipated within 4 hours of drug administration. On the other hand, Schmidt (1987) has shown that MDMA

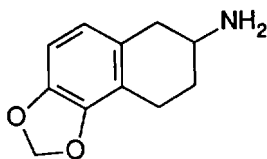


FIGURE 13. *Tetralin analogue of MDMA that lacks MDMA-like effects*

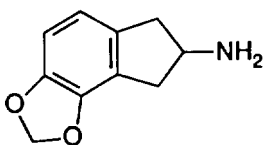


FIGURE 14. *Indan analogue of MDMA that lacks MDMA-like effects*

TABLE 5. *Drug discrimination results: Substitution tests in MDMA-trained rats*

Compound	Result in MDMA-Trained Rats
Figure 11	CS ED ₅₀ =1.29 mg/kg
Figure 12	CS ED ₅₀ =0.59 mg/kg
Figure 13	PS (75% drug responding @ 1.75 mg/kg)
Figure 14	PS (67% drug responding @ 0.5 mg/kg)

KEY: (±)-MDMA.HCl, 1.75 mg/kg IP, CS=complete substitution; PS=partial substitution.

has a biphasic depleting effect on cortical serotonin, with the later phase (more than 6 hours) associated with the long-term toxicity, a toxicity blocked by fluoxetine. Schmidt and Taylor (1987) administered the serotonin uptake inhibitor fluoxetine to rats 3 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 own studies, cited above, we have shown that fluoxetine does not antagonize the MDMA cue. Battaglia et al. (1988) 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 presumably a reflection of neuron terminal degeneration. These studies indicate that the acute pharmacology can be dissociated from the long-term neurotoxic effects of MDMA.

Further, it is also known from work with the neurotoxin PCA that some structural congeners have an acute depleting effect on brain 5-HT, but lack the long-term neurotoxicity that is characteristic of PCA (Fuller et al. 1977). 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 clearer definition of the primary pharmacology of entactogens. 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.

DISCUSSION

QUESTION: What are the criteria that you used for these newer compounds in order to classify these newer drugs as either sympathomimetic or hallucinogenic?

ANSWER: We are basically forced to deal with a variety of models. First of all, we have LSD-trained rats, and we have used that as our general screen for hallucinogen-like activity. If you are familiar with the drug discrimination literature, you can get false-positives, and perhaps Professor Glennon will correct me if I am wrong, but I am not aware of false-negatives. There are no cases where, in the drug discrimination paradigm, an animal has said this drug is not hallucinogenic when, in fact, in humans it is known that it is. So my feeling with drug discrimination is that we are detecting false-positives.

We are using I-125-labeled DOI as a radioligand and that has been shown, particularly by Professor Glennon and his coworkers, to be a good model for hallucinogenic activity. I think 5-HT₂ agonists, in terms of biochemical pharmacology, are the clearest indication that a compound is hallucinogenic.

We are routinely screening compounds for ability to displace I-125 DOI from frontal cortex homogenates. As far as the CNS stimulant effects, differentiating from psychostimulants, the present model we are using is substitution in amphetamine-trained rats, in drug discrimination. We have used synaptosomes and looked at their effect on dopamine release and reuptake. But basically they are correlative models.

And it is certainly true that these compounds could well be hallucinogenic but fall outside what we understand the structure-activity relationships of these compounds to be. For example, it may well be that MBDB in humans at some dose is hallucinogenic and is acting by some mechanism that is totally different from what we understand to be the mechanism of mescaline, DOM, or LSD. But at the present time, based on what we understand about structure-activity relationships, it should not be. That remains to be seen.

COMMENT: It might be advisable to stick to more operational definitions in talking about these compounds. One runs a risk if compounds have not been tested in people, and to refer to a compound as hallucinogenic when it is operative. A drug discrimination test might lead you to certain assumptions about the drug that are not true.

RESPONSE: Generally, it is safest to say there is LSD-like activity in drug discrimination profiles. Similarly, with these so-called entactogens, the name we have given them, we do know that we find in the tetralins and indans, for example, that a particular amino-indan we tested has fairly high potency in substituting for MDMA or MBDB. But we do not know what its effects would be in humans. There is no way to test that. Basically we are trying to develop correlative models based on what we know from the clinical data. But, again, it is speculative in the absence of clinical studies.

COMMENT: I would not rule out the possibility that MDMA or MDA produces effects at serotonin-2 receptors. Some of the data that I believe Dr. Battaglia has accumulated shows that of the 20 brain recognition sites that we have looked at, using standard radioligand binding procedures, MDMA has the highest affinity at serotonin-2 receptors as labeled by tritiated DOB. But I must qualify that. If you compare MDMA to something like DOI, it is about a hundredfold weaker. But its affinity is still 100 nanomolar in terms of an IC_{50} , concentration, which is still relatively potent considering the concentrations that may be achieved in brain at some of the doses used in animals.

RESPONSE: I have tended to think that things do not have affinity unless we see low nanomolar affinity. I think the EEG studies are fairly revealing in that regard. The fact that we see this increase in alpha-1 power in the striatum is a characteristic of 5-HT₂ agonists. And we are clearly seeing EEG effects at doses that are not increasing that power in the alpha-1 frequency. I tend to think that 5-HT₂ agonist effects are not that important in the action of these compounds.

COMMENT/QUESTION: I was very intrigued by your substitution data from the drug discrimination paradigm. But my question is not unlike Lou Seiden's. For with substances that are characterized by tremendously qualitatively different effects, biphasic in nature, and in many functional

assessments, I feel it may be premature to zero in on one selected training dose and give that a label.

I would like to know whether or not you have explored minimal discriminational doses of MDMA or MBDB and whether you have contrasted them with higher doses and have done experiments that are reminiscent of the Appel and White type approach where different mechanisms kick in at different dose ranges of the drug. Do we cover the relevant qualitatively different effects with that technique and with that approach, where one is zeroing in on one amphetamine dose and one MDMA dose?

I also have another question. When you compare release data from a slice preparation where it is in one application with discrimination data, are you comparing a creature that has received hundreds of injections every other day, on the average? I do not know what your protocol looks like, but I presume every other day is a drug and every other day is a control condition. Here you have an acute preparation and the relationship, of course, is quite tenuous.

ANSWER: Yes. We have looked at the lower doses of MDMA; the 1.75 mg/kg is the dose that gave us the best discriminability. We tried initially to train with 1 mg/kg but could not. We continued to increase the training dose by increments until we found the dose where we got reliable discrimination. It was 1.75 mg/kg. At least in our paradigm, I do not see how we could go much lower.

We have not explored all of the dose-response relationships. And with respect to the nature of the cue, we have studies underway now with a variety of serotonin agonists and antagonists, for example, fluoxetine. And have looked at MDMA. We cannot block the cue with fluoxetine. We are also looking at 8-hydroxy-DPAT, buspirone. PCPA pretreatment is on the way. So there are a variety of manipulations that we have in process. The treatments are all randomized, so a lot of them are only half finished, and no one can say what is happening. But in terms of pinning it down, I think that needs to be done.

We are looking at biochemical models as really pointing us in a particular direction. They are not rigorous; I recognize that. If we focused all our attention on drug discrimination we could do some complete studies. My emphasis in medicinal chemistry is to explore structure-activity relationships and synthesize tools to explore how the drugs work. So we basically, more than focusing on pharmacological rigor, have tried to find quick screens that would point us in a direction so we could synthesize a drug to test this hypothesis.

Ultimately, these compounds will require a good deal of pharmacological evaluation, and we are in the early stages of that. In accordance with

Dr. Gibb's hypothesis regarding dopamine involvement, we thought that perhaps MBDB would not be neurotoxic because of a lack of effect on dopamine. But, in fact, it is neurotoxic as well, measured by whole-brain serotonin 5-HIAA and tritiated paroxetine binding sites. It is perhaps two-thirds the toxicity, on a molecular weight basis, of MDMA, but it is toxic.

A number of the studies that we have done are not completely rigorous, but their purpose is to see whether neurotoxicity is related to the nature of the cue. Your questions are well taken, but it has really been a choice between economy and rigor so that we could find the chemical structure to synthesize.

COMMENT/QUESTION: You have answered the first question, which was on the issue of whether or not MBDB produced long-term effects on the amine system. The second question has to do with the nature of the cue.

We have talked with people who participated in our study over the last year. As you know, many of them have experimented with a wide variety of psychoactive drugs, including MBDB. When asked about MBDB their response seems to be lukewarm in terms of how it compares to subjective effects, and whether these effects are comparable to those of MDMA. Is that accurate?

ANSWER: When we decided to make MBDB we felt the alpha-ethyl would attenuate hallucinogenic activity. Dr. Shulgin made that compound because he was looking at things that had a stimulant effect. He had made it but had not evaluated it at effective doses. After a discussion, he evaluated it in the group of people that worked with him.

Basically, the consensus was that the psychopharmacology was similar but that the compound lacked the ability to produce the kind of euphoria produced by MDMA. And he reported that there were at least one or two individuals who felt they never wanted to take the compound again.

My own bias is toward the therapeutic potential. I do not care whether anything we develop produces euphoria or dependence potential. I think from the point of view of a drug abuse problem or a dependence liability that the alpha-ethyl probably does not have the reinforcing qualities and is not as pleasurable as MDMA.

COMMENT: My question to these people would be directed toward this quality they regard as unique for MDMA--this rush. They admit that that is not the main reason for taking it. They do seem to be able to make that distinction. They do not dispute the fact that they enjoy the rush from an MDMA dose. Whatever this other quality is, they recognize it. And it is that quality that was less apparent in MBDB than in MDMA.

RESPONSE: I think this is an area where you would have to do detailed double-blind crossover studies and some fairly extensive testing to map out what the nature of that effect is.

In the drug discrimination assay we get symmetrical transfer. They seem to be the same. And the consensus, at least from Dr. Shulgin's group, is that it generally has the same kind of effect. Obviously it has not become a problem on the street. And I think if it was a very desirable compound we might well have heard something about it.

QUESTION: Have you done any studies of the metabolism of these compounds? As you probably know, there have been reports that MDMA is very quickly metabolized into MDA. Have you looked at MBDB to see if the ethyl group gets cleaved so that you essentially have an MDMA compound after you are through?

ANSWER: There is no chemical precedent for that kind of transformation. I really cannot think of an enzyme system that would cleave that down to the alpha-methyl. I think the effect is due to the alpha-ethyl.

In terms of other sites of metabolism, we are looking at the metabolism in the dioxole ring and in dealkylation. We have seen some interesting things, but I could not comment on this right now. With respect to the alpha-ethyl, I think that the parent compound is probably the one that is active.

QUESTION: I have two questions about your MBDB discrimination studies. It sounds as though you are doing experiments to investigate whether neuronal stores of serotonin are required for MBDB to be recognized. You mentioned that fluoxetine did not prevent the recognition. Does it prevent the release of serotonin *in vitro*? In other words, is that a carrier-dependent release by MBDB as it is, for example, in the case of *p*-toluylamphetamine?

My second question is this: You mentioned fenfluramine. I presume you used the racemic mixture, which would mean that in the brain you would have both *R* and *S* fenfluramine and *R* and *S* norfenfluramine present. And since these differ widely in their effects on dopamine versus serotonin neuronal systems, have you studied individual enantiomers of either fenfluramine or norfenfluramine?

ANSWER: Actually we used synthesized (+)-fenfluramine. The fluoxetine story is not clear. It does not block the discriminative cue, but other workers have shown that it blocks the neurotoxicity. We have not looked at it in enough detail or at any of the *in vitro* models to see whether it blocks or releases serotonin.

COMMENT: It seems as though that might be a good tool to determine whether the discrimination really does relate to serotonin release because, clearly, it has been shown to block the serotonin release *in vivo*. If it does not block the drug discrimination it seems that it is not consistent with the idea that that is a consequence of serotonin release.

RESPONSE: When you are in this business, you get letters from many strange people. I received an unsolicited letter from a fellow in Geneva, Switzerland, about a year ago, who told me that he had taken fluvoxamine, which I believe is available clinically in Geneva, and had subsequently taken MDMA. He said that the fluvoxamine had no effect on the action of the MDMA. I think this is an interesting question which, at least in one anecdotal account, suggests that there is a difference.

The biochemical followup would be interesting if it does prevent the release. And maybe the serotonin is a red herring. But that is the only thing we have seen consistently at this point

COMMENT [DR. SCHUSTER]: I am extremely pleased to see the sophistication of the animal studies and the medicinal chemistry studies. I lament the current lack of sophistication with regard to the available data in humans. It is feasible, as my colleagues and others have shown, to train drug discrimination in humans-to do as precise quantitative work there as is done in animals. In fact, probably more precise.

As far as subjective effects are concerned, and people's responses regarding why they take drugs, I have to say that I have a fair degree of skepticism that people are reporting in any way what is relevant. It may be, it may not be. But I can assure you that the contingencies that shape verbal behavior may be very different from the contingencies that shape the drug-taking behavior. And as a consequence there may not be any necessary correlation.

It is unfortunate, and this is a real deficit in this field, that we cannot do the very human studies that I know you would all like to do and, therefore, we rely upon whatever evidence we have to reach conclusions. But we have to be wary of the fact that the human data are weak in comparison.

QUESTION: Have you made any attempt to antagonize the MBDB stimulus with serotonin antagonists?

ANSWER: We have tried ketanserin, but it did not antagonize the stimulus. I do not believe we have tested fluoxetine in the MBDB-trained animals. It has only been tested in the MDMA-trained animals. We have not found an antagonist to the cue yet.

QUESTION: Did you measure tryptophan hydroxylase or just the 5-HT/5-HIAA depletion?

ANSWER: We used it in the 20 mg/kg twice a day for a 4-day regimen with MDMA, and then corrected for molecular weight and used an equimolar dose of MBDB, sacrificed the animals 2 weeks later, and then measured. We used basically HPLC and used serotonin and 5-HIAA from one hemisphere and then measured tritiated pyroxetine from the other hemisphere. And we got something like 60 percent depletion of serotonin, and the pyroxetine binding site $B_{\max}$ decreased by about 60 percent. With MBDB it was decreased by about 40 percent. It was a clear and significant decrease, but not quite to the extent that we had. But we have not looked at tryptophan hydroxylase.

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ACKNOWLEDGMENTS

This research was supported in part by U.S. Public Health Service grant DA 02189 from the National Institute on Drug Abuse and Biomedical Research Support Grant 2-S07-RR05586-18 from the Division of Research Resources.

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