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Evaluation of 3,4-Methylenedioxyamphetamine (MDA) as an Adjunct to Psychotherapy

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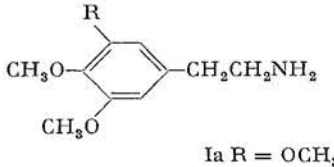
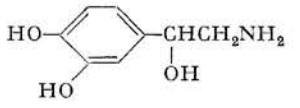
The alkaloid mescaline (Ia), the principal active component of the cactus Peyotl *(Lophophora williamsii),* is one of the oldest, simplest, and best studied of all the known psychotomimetic chemicals. Its close resemblance to the natural neurotransmitter norepinephrine (II) has suggested that the mechanism of function of these two materials may have some points in common in their action upon the human nervous system. A chemical of intermediate structure, 3,4-dimethoxyphenethylamine (DMPEA, Ib), lacks one of methoxyl groups of mescaline. Interest in his base was kindled by the observation of its presence in the urine of schizophrenic patients, but not in that of normal subjects (*Friedhoff* and *Van Winkle* [6]. This chemical is most probably not an endogenous psychotogen, for evaluation of it in human subjects by *Hollister* and *Friedhoff* [8] and *Shulgin et al.* [16] revealed neither psychotropic nor sympathomimetic properties.



Ia R = OCH_3
b R = H



II

The addition of an α-methyl group to the side chain (to provide a structure analogous to amphetamine) has been shown in a number of experiments to influence both qualitatively and quan-

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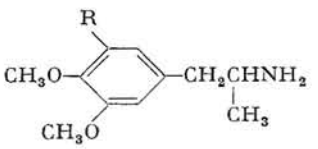
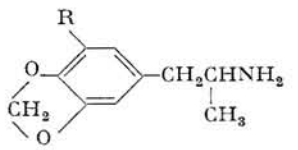
titatively the psychotropic properties observed. The α-methyl homolog of mescaline is TMA (III a); it displays psychotomimetic properties much like those of mescaline but is approximately twice as potent (*Peretz et al.* [12]; *Shulgin et al.* [13]). The analogous two-methoxy counterpart (III b) has been reported to have produced 'mescaline-like' effects at levels of 10 mg/kg in one of two psychiatric patients (*Fairchild* [4]). Investigations by *Alles* (*Fairchild* [5]) at a lower level of 1.4 mg/kg showed only minor autonomic changes and no subjective phenomena or perceptual alterations.



IIIa R = OCH_3
b R = H



IVa R = OCH_3
b R = H

The replacement of two vicinal methoxyl groups by a methylenedioxy ring reasonably followed from the frequent concomitancy of these systems in the plant world. The methylenedioxy analog of TMA (i.e., MMDA, IV a) was shown to elicit a syndrome comparable to mescaline in the production of imagery (*Shulgin* [14]), but different in the absence of depersonalization or of perceptual distortions. It has been shown to be useful in the facilitation of certain psychotherapeutic procedures (*Naranjo* [11]). The two-oxygen analog, 3,4-methylenedioxyamphetamine (MDA, IV b) would, on the basis of the above analogies, be expected both to lack the potency by weight of its three-oxygen counterpart, and not to evoke as intense a psychotomimetic response. In biochemical (*Mann* and *Quastel* [10]) and pharmacological (*Gunn et al.* [7]; *Benington et al.* [2]; *Alles* [1]) studies in various animal species, MDA has been compared with amphetamine. At high dose levels in cats, effects were observed that suggested psychotomimetic properties.

Only three reports are available that refer to the investigation of MDA in human subjects. One has described the production of increased rigidity through an unspecified dosage in one case of Parkinson's disease (*Loman et al.* [9]). A study was made of the

levo-isomer of MDA as an anorexigenic agent (*Cook* and *Fellows* [3]), and it was noted in clinical trials with obese patients that levels up to 120 mg/day produced unpleasant CNS effects (*Shulgin* [15]). The report of *Alles* [1] is the first study in which an attempt at subjective evaluation of psychotropic properties was made. Here direct comparisons of MDA were made with amphetamine at oral levels between 60 and 120 mg. The threshold for a 'real subjective central effect' was about 60 mg total dose, although there was neither the change of mood nor the sleeplessness that was found characteristic for some one-fourth this amount of amphetamine. At higher levels (maximum 126 mg) there were observed distinct visual and related sensory changes (peripheral field changes and possibly auditory hyperacuity), although there were no color or hallucinogenic effects, and only minor autonomic symptoms.

These preliminary studies suggested that this compound had a potential for producing changes in affective mood and mild depersonalization; i.e., a psychotropic effect free of the visual and auditory distortions which regularly occur with other hallucinogens. An evaluation of this material in a selection of normal human volunteers is the subject of this report.

Method

MDA was administered orally, as the hydrochloride salt, to eight volunteers who had on previous occasions experienced the effects of LSD under conditions comparable to those in the present experiment. It was explained to them that MDA might well have the effects of a hallucinogen, and that records would be made of their subjective experiences and of their comments upon how this experience compared to that under LSD. All of the subjects were interviewed on their life histories and on their interest in experimentation with psychotomimetic compounds. Close observation was maintained during the complete time of the drug's effect, and thus a sympathetic audience was available if a subject wanted to discuss personal or symptomatic problems; otherwise the experimental situation was left largely unstructured. There were six MDA sessions in all: four of these involved one person only, the other two were with married couples. At one point or another in all sessions the volunteers were asked to look at objects, at their hands, at a mirror and at other people in order to detect perceptual distortions. They were also asked to close their eyes and attend to possible imagery and to report their ongoing feelings and body sensations. For the rest of the time, they were encouraged to relax, to be at ease, and to spend the time as they wished.

The dose of MDA was 150 mg in the last five sessions. In the first session, involving one of the couples, each received 40 mg, and one partner was given an additional 40 mg after the first hour.

Results

In spite of the expectation that MDA would be a hallucinogen, none of the subjects reported hallucinations, perceptual distortions, or eye-closed imagery within the dosages employed. Yet a similarity was pointed out by all participants between MDA and their previous experience with LSD. It was stated that both drugs had brought about an intensification of feelings, a facilitation of self-insight, a heightened empathy or aesthetic enjoyment at some point during the intoxication. The effects of MDA were noted by all subjects between 40 and 60 minutes after ingestion. The subjective effect of the drug reached its peak within thirty minutes of the beginning of symptoms, and lasted for approximately eight hours. These symptoms were clearly and unequivocally recognized by the subjects on the basis of their previous experiences with similar drugs. The only conspicuous physical symptom was moderate mydriasis, and this was constant.

Of the four single subjects, one spent much time writing on certain aspects of his life history, which he now wanted to understand better. Each of the remaining three interacted very actively within his experimental situation, and reported waves of euphoria and of depression or guilt throughout his session. In either state most of their concern was with their own life and personality.

For both of the married couples the session was a fruitful one in terms of achieving better communications and mutual acceptance, and much time was spent in the discussions of common difficulties. For seven of the eight subjects, music was perceived with 'three-dimensionality' as is often reported with the hallucinogens.

There was amnesia for some episodes in the sessions of both married women. This is remarkable in that neither of them is aware of amnesia in other circumstances (including three LSD sessions); they appear to be healthy psychologically and for one of them the MDA intoxication must be held as being subjectively slight, with a total dose of only 40 mg. The amnesia appeared to be temporary, however; a few days later, most of the session could be recalled with the assistance of the therapist.

Discussion

On the whole, judging from the previous reports and from the results of the studies here, the effects of MDA appear to be *sui generis:* it affects the feelings in a way which is comparable to that observed with hallucinogens, but it does not bring about the perceptual phenomena, depersonalization, or disturbances of thought which characterize those substances. Further, there is little evidence of the peripheral sympathomimetic effects of amphetamine. It is suggested therefore that this compound may be of value in the facilitation of psychotherapy, by virtue of its ability to enhance access to feelings and emotions without the distractions of sensory distortion. In instances of such usage, attention must be directed to the occasional possibility of amnesia, and constant attendance during psychotherapy is advised.

Summary

Consideration of structure-activity relationships of known hallucinogens suggested that 3,4-methylenedioxyamphetamine (MDA) might produce psychotomimetic effects in humans. In a series of trials in eight subjects, doses of 150 mg of MDA produced none of the perceptual alterations or the depersonalization which had been anticipated, but it did cause heightened affect, emotional empathy and access to feelings which suggested that MDA may be a useful drug if utilized as an adjunct to psychotherapy.

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