Stereospecific Actions of DOET (2,5-Dimethoxy-4-Ethylamphetamine) in Man

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Several different molecular conformations of psychedelic drugs have been proposed to explain the very similar effects of drugs with markedly divergent chemical structures, such as mescaline and *d*-lysergic acid diethylamide (LSD). In some of these models, the α-carbon of methoxyamphetamine psychedelics approximates the asymmetric carbon No. 5 of LSD predicting that the (−) "R" isomer of the methoxyamphetamines should possess greater psychedelic activity than the (+) "S" isomer.

The present study reports a comparison of the psychotropic effects of isomers of DOET (2,5-dimethoxy-4-ethylamphetamine) a "psychedelic" methoxyamphetamine, in normal human subjects. The (−) "R" isomer is about four times as potent as the (+) "S" isomer, thus specifying the psychoactive conformation of the drug. This clinical study represents a novel approach to determining the molecular conformation of a drug at its receptor site.

One of the most puzzling aspects of research into psychedelic drug action revolves on the fact that compounds of highly dissimilar chemical structure exert common subjective effects in man. For example, the psychological effects of mescaline, a phenethylamine derivative, closely resemble those induced by *d*-lysergic acid diethylamide (LSD), a complex multiringed indole derivative; the effects of mescaline, however, differ markedly from those of amphetamine, which does resemble mescaline chemically. The psychedelic actions of LSD, mescaline, and related drugs involve a characteristic concatenation of perceptual and cognitive changes that are quite distinct from psychotomimetic effects that can be elicited by high doses of amphetamine.

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All of the drugs that produce psychedelic effects, including LSD, several tryptamine derivatives, mescaline, and several methoxyamphetamines, appear to act at the same or very similar receptor sites in the brain. Thus, psychedelic drugs, though of different chemical classes, all exhibit mutual crosstolerance, while no crosstolerance develops between drugs such as mescaline and a nonpsychedelic drug such as amphetamine.[1-3] Further, in minute doses, LSD suppresses the firing of serotonin cells in the brain stem, an effect shared by psychedelic drugs but not manifested by other drugs.[4] However, LSD and mescaline do differ somewhat in their effects on serotonin metabolism[3] and raphe cell firing.[4]

Several hypotheses have been advanced to explain how phenethylamine derivatives such as mescaline and the methoxyamphetamines might assume a conformation analogous to the indole portion of tryptamines.[5] An alternative possibility, explaining the disparate actions of numerous methoxyamphetamines,[6] postulated that the side chain of phenethylamines and methoxyamphetamines might assume a position approximating the C-ring of LSD.[7,8] However, neither of these suggested conformations would be favored energetically in solution, so that several workers[9-12] have proposed a different conformation for psychedelic phenethylamines and methoxyamphetamines that is energetically more stable (Figure).

Is it possible to distinguish among these alternatives? In the conformation specified Chothia and Pauling[9] and others,[10-12] the side chain amine and α-carbons of phenethylamine and methoxyamphetamine psychedelic drugs correspond to positions No. 5 and 6 respectively of LSD. Of the four known stereoisomers of LSD, essentially all psychedelic activity resides in (+)-LSD, in which the configuration at both carbons No. 5 and 8 is "R."[13] The designations (+) and (−) refer to the direction in which a chemical rotates a beam of polarized light, while "R" (*rectus*) and "S" (*sinister*) describe absolute stereo-

configuration. While there are no stereoisomeric forms of the phenethylamine drug mescaline, the psychedelic methoxyamphetamines can exist in two configurations, of which the (−)-isomer possesses the "R" configuration. According to the Chothia and Pauling model, the (−)-isomer of methoxyamphetamines corresponds to the psychedelically active (+)-LSD and accordingly would be expected to be the more active psychedelic agent. The hypotheses that phenethylamine and methoxyamphetamine conformations resemble the indole moiety[5] or C-ring[7,8] of LSD do not equate the position of the α-carbon with carbon No. 5 of LSD and, therefore, do not predict any difference in psychedelic activity of methoxyamphetamine isomers. Thus, a comparison of the psychedelic activity of the isomers of a methoxyamphetamine may provide information bearing on the conformation of these drugs at their receptor sites in the brain.

DOET (2,5-dimethoxy-4-ethylamphetamine) is a methoxyamphetamine analogue of mescaline; in its racemic (±) form, it is many times more potent than mescaline in eliciting psychedelic-type effects in man.[14,15] Recently, the (+)- and (−)-isomers of DOET were separately synthesized and shown to represent the "S" and "R" configurations, respectively,[16] rendering them directly relevant to the issues reviewed above. Hence, a comparison of the psychotropic activity of the (+)- and (−)-isomers of DOET in man was implemented.

Methods

Ten subjects served in the experiment, two women and eight men, ages 26 to 32 years. All were psychiatry residents at the University of Maryland Hospital. All ten subjects had previously smoked marihuana and five had taken LSD on at least one occasion. None were frequent users of these drugs.

The design, random, double-blind throughout, proceeded in stages under the direction of the Chief of the Section on Research Design and Methodology of the Maryland Psychiatric Research Center (RB). Initially, eight subjects were utilized to explore and compare the effects of 1 and 2 mg of (+)-DOET, 1 and 2 mg of (−)-DOET, 2 and 4 mg of (±)-DOET, and an inert placebo. In this phase, each subject received three of the above possibilities on separate days at intervals of at least one week. The blind was broken at the conclusion of this set of 24 trials and it was revealed that the (+)-isomer at doses of 1 and 2 mg had been without detectable effects. Two additional subjects were then recruited to receive 3 and 4 mg doses of (+)-DOET randomly incorporated in a three trial series. When it eventuated that the subject receiving the 4 mg dose of (+)-DOET showed a "definite reaction," four of the earlier subjects served on one more occasion each, receiving either 4 mg of (+)-DOET or placebo. In sum, ten subjects were utilized for 34 drug administrations. All DOET dosages were computed as the hydrochloride, and were formulated in identical clear gelatin capsules with kaolin filler.

Subjects were fully informed as to the nature of the experiment. All sessions were accomplished at the Maryland Psychiatric Research Center in a quiet, comfortable room, containing a couch for the subject to recline on if desired, an easy chair, plants, a variety of objects of art, food, a record player, head phones, and records. All drug capsules were administered at 9:30 AM, with the subjects fasting since the preceding midnight. For the following 8 to 12 hours, subjects were under the direct and continuous supervision of one of the authors (S.U.), who has had considerable experience in observing psychedelic drug effects.[17,18] Immediately after drug ingestion and four hours later, at the approximate peak of drug action, pulse and blood pressure were monitored and a variety of psychological tests were administered: the Lorr Outpatient Mood Scale, Outpatient Symptom Check List, Hildreth Current Reaction Scales, and the Block Design and Digit Span subtests of the Wechsler Adult Intelligence Scale. Urine specimens were collected at 0, 3, 6, 9, 12, and 24 hours. Additionally, toward the end of the session, a semistructured, tape-recorded interview was conducted, covering the range of subjective reactions that might have occurred during the day and specifically probing for changes in feeling states, in sensory experience in all modalities, and in cognitive processes. Finally, the experimenter, who had spent the entire day in company with, testing and interviewing the subjects, and who was blind as to whether the drug or placebo, or which drug had been administered, at the conclusion of each session day, recorded his assessment of the subjects' responses into one of the four predetermined categories: 0="no discernible reaction"; 1="mild reaction, subject certain of drug effects"; and 3="intense reaction, including eyes-closed visual imagery and definite amplification of feelings." It may be noted here that the mood and symptom checklist data proved of questionable relevance; hence, the principal data on which the present report is based are constituted by the experimenter's rating. Results obtained with the other procedures will be reported separately.

Comparative Subjective Effects of DOET Isomers and Placebo

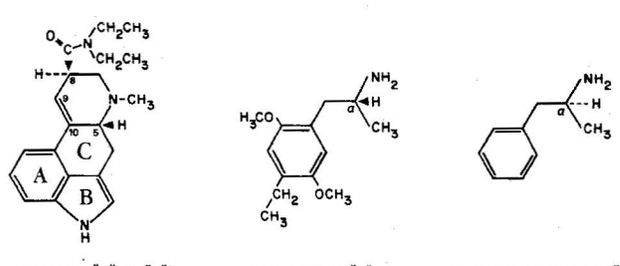
		Drug Condition and Dosage							
		(+)-DOET				(−)-DOET		(±)-DOET	
Subjects	Placebo	1 mg	2 mg	3 mg	4 mg	1 mg	2 mg	2 mg	4 mg
1	0*				2		3	2	
2		0				1			3
3			0		2	2			2
4		0					3	2	
5	0,0					2			3
6			0				2	0	
7	0				0		3	2	
8	0					0			1
9				0		0			1
10					2	2	3		
Means†	0	0	0	0	1.5	1.17	2.8	1.5	2.0

* Code: 0, No discernible reaction. 1, Mild reaction, not subjectively certain. 2, Definite reaction, subjectively certain. 3, Intense reaction, including imagery and amplification of feelings.

† The mean value for 2 mg of (−)-DOET differs significantly from the means for 4 mg of (+)-DOET ($P < .05$), 1 mg of (−)-DOET ($P < .01$), and 2 mg of (±)-DOET ($P < .05$). No other comparisons are significantly different.

Results

Relative Potency of Isomers.—The Table reflects the reac-



Possible conformations of LSD, amphetamine, and DOET (2,5-dimethoxy-4-ethylamphetamine) with their asymmetric carbons superimposed.

tion of each subject to each drug administration. Placebo administrations did not produce any subjective response, nor was any discernible reaction noted with 1, 2, or 3 mg of (+)-DOET. At 4 mg, three of the four subjects showed a definite, subjectively certain reaction to (+)-DOET; one was nonreactive. In contrast, four of six subjects receiving 1 mg of (−)-DOET showed definite drug reactions. At 2 mg of (−)-DOET, this reaction was intense in four of five subjects and definite, though not intense in the fifth. The intensity of drug reaction to 2 and 4 mg of (±)-DOET tended to resemble reactions to 1 and 2 mg of (−)-DOET, respectively.

Thus, 1 mg of (−)-DOET appears to correspond in potency to 2 mg of (±)-DOET, and 2 mg of (−)-DOET to 4 mg of (±)-DOET. Further, 1 mg of (−)-DOET appears equivalent in psychotropic activity to 4 mg of (+)-DOET, with 2 mg of (−)-DOET producing clearly more intense effects than 4 mg of (+)-DOET. Accordingly, (−)-DOET seems to be about four times more potent on a milligram basis than (+)-DOET, and can account in major part for the psychotropic activity of the racemic form of the drug.

It may be noted that drug responsivity was fairly consistent across trials intraindividually, though there was interindividual variation with some subjects tending to give low responses under all drug conditions. Subject 6, for instance, who responded least of five subjects to 2 mg of (−)-DOET, also exhibited the least response to 2 mg of (±)-DOET. Similarly, subjects 8 and 9, who manifested the least response to 1 mg of (−)-DOET, also gave the smallest response to 4 mg of (±)-DOET.

Interestingly, the stereospecific preference for psychedelic activity of a methoxy derivative of amphetamine is opposite that of the central stimulant effects of amphetamine itself, for which the (+) "S" isomer is more potent.[19] In this regard, we were alert to possible amphetamine-like central stimulant actions that might be displayed by low doses of the (+)- but not the (−)-isomer of DOET. However, no clear-cut amphetamine-like stimulant actions of either DOET isomer or of the racemic mixture were detected.

Subjective Effects.—In the present study, the quality of subjective effects elicited by the isomers of DOET was largely similar to those previously obtained with the racemic form of the drug administered in a more neutral experimental setting; this was also the case with regard to the stability of pulse and blood pressure and the absence of measurable changes in performance on tests of intellectual functioning.[14,15] The onset of drug action tended to be very gradual, 1½ to 3 hours after ingestion, with an earlier onset at higher doses. Effects peaked at four to five hours and subsided at six to ten hours.

The principal and most common effects were reported as "enhanced" perception in all modalities and combined with a difficult-to-describe cognitive alteration communicated by one subject on 4 mg of (±)-DOET, as follows: "I was not just perceiving things, I felt more continuous with the things I was experiencing. I don't think I ever completely lost my sense of self, but it was much diminished."

In the affective domain, the drug action appeared to be quite different depending on whether the subject was paying eyes-open attention to the external environment in which case affect was not as prominent, or listening to music with eyes closed, in which case clearly amplified feelings would develop. These points are perhaps best illustrated in the retrospective reconstruction by one subject of a (±) 4 mg experience:

> Before the experiment, I was not in the best of moods. I was annoyed, depressed, washed out. The onset of the drug effect was fairly definite, and like the first time, was associated with a sense of bodily relaxation. From that point on, my mood throughout the day was better than it was when I had come in. After a while, I just followed the drift of what the music did to me. It was very easy to get sucked into the feelings. At one point, I was crying, really in many respects out of joy. I was moved, put it that way. It was at least moderately profound. When my eyes were open and we were talking, there was not much effect that I could tell. But while I was closing my eyes and the music was on, I was flowing into different moods rather quickly. And that was pretty intense.

Most subjects, with eyes open, described a condition of relaxed well-being that contrasts with the more stimulated euphoria associated with amphetamine. For instance, one subject, on 2 mg of (−)-DOET, remarked as follows: "Primarily I had this feeling of a very marked relaxation . . . this steady feeling of well-being . . . it wasn't a speedy or panicky kind of thing, but like, hey, everything is all right." Another subject on 1 mg of (−)-DOET remarked, "I feel really good, peaceful. My body feels supergood . . . no tensions in any muscles anywhere, which is quite unusual."

As indicated, apparent enhancement of perception in one or more sensory modalities was commonly noted. For instance, one subject on 2 mg of (−)-DOET said, "The food, the almonds were really supertasty. I couldn't believe it when I first tasted one." Another subject on 2 mg of the (−)-isomer commented, "There seemed to be more definition and more distinctness about things in my visual field. Lights seemed to be brighter. Eating the food—I really was getting into the food." Still another subject, on 2 mg of (±)-DOET reported:

> Sensory kinds of things are definitely different. Looking around the room, it just takes on all sorts of increased meaning. Eating—I could taste more distinctly, the blend goes together more smoothly. Clasping my hands together, I can feel my fingers pressing against one another in a heightened way. It's all a very pleasurable kind of experience. Listening to music-again, it is difficult to describe, hearing what it is more clearly, more meaningfully, more fully.

No hallucinogenic effects or distortions of visual perception were detected in any subjects with eyes opened. Several subjects described vivid imagery when they closed their eyes. For instance, one subject under the influence of 2 mg of (−)-DOET said, "I could close my eyes and create very vividly any sorts of images that I wanted to." A subject on 4 mg of (+)-DOET described, "I had vivid imagery when I closed my eyes. My fantasy seemed very real to me."

No subject displayed psychotomimetic effects at any dose. Although there was occasional transient anxiety, all were lucid and coherent throughout the times of testing and interviewing. In fact, rather than any loss of insight, subjects commonly reported feeling more depth or clarity of self-awareness during those periods when attention

was focused on inner experience. For instance, on 1 mg of (−)-DOET, one subject said, "I was feeling very much in touch with feelings, the potential for joy, the potential for sadness. I did a lot of thinking about myself, like self-acceptance and different things like that." The overwhelming majority of reactions were described in positive terms; although, in this regard, it should be noted that the physical and interpersonal context of the experiment was expressly intended to facilitate pleasant, or interesting sessions, or both. In the low-dose range, only one subject found the effects of the drug unattractive, reporting on his 2 mg racemic sessions as follows: "I would describe the effect on me as being tired, drowsy, with some uncertainty, some anxiety, experiencing myself as not being up to par; the total subjective state was not perhaps actively distressed, just unattractive." In the high-dose range, this subject was again unique in the predominantly negative affective quality that characterized his 2 mg (−)-DOET session, he stated: "Feelings were a lot stronger. I think the drug brings a lot of things to a sharper focus, makes them more vividly real. I think I have been much more in touch with things that for me were easier not to attend to, but under the drug they were there."

Unlike other methoxyamphetamines, psychotomimetic and hallucinogenic effects have not yet been demonstrated with DOET.[14,15] This may be related to the low doses employed in clinical trials thus far and possibly to a somewhat different dose-response slope as compared with other psychedelic agents.[15] However, the chemical structure of DOET, as well as its psychological effects, indicate that DOET is fundamentally quite similar to other psychedelic drugs.

Comment

The present results indicate a clear-cut stereospecific preference for the (−) "R" isomer of DOET in eliciting apparent psychedelic effects. Recently, in a preliminary human evaluation, Shulgin[10] reported that (−)-DOM (2,5-dimethoxy-4-methylamphetamine) is more potent in its psychotropic action than the (+)-isomer. DOM, the methyl analogue of DOET, became an item of abuse in the drug culture under the designation of STP.[20] In rats, (−)-DOM is about four times more potent than (+)-DOM in altering conditioned avoidance behavior, while (−)-DOB (2,5-dimethoxy-4-bromoamphetamine), the bromine analogue of DOET, is about four times more potent than (+)-DOB.[21] In causing contraction of umbilical artery strips of sheep, the (−)-isomers of DOM, DOET, and DOB are four times as potent as the (+)-isomers.[22] The animal studies obviously closely parallel our findings in humans. All these results taken together tend to confirm a general stereospecific difference in methoxyamphetamine isomers.

It is conceivable that the discrepant potencies of DOET isomers reflect variations in metabolic disposition. The best known enzymatic alteration of phenylethylamines responding to stereospecific variations at the α-carbon is β-hydroxylation. The β-hydroxylation takes place primarily in sympathetic nerve terminals and is unlikely to represent a quantitatively major pathway of DOET degradation.

Since the "R" configuration at the α-carbon of the methoxyamphetamines corresponds to the "R" configuration of carbon No. 5 in the most potent isomer of LSD, it appears likely that methoxyamphetamines do assume a conformation at the psychedelic receptor sites in the brain similar to that which would place the α-carbon of methoxyamphetamines in the same or a very similar position as carbon No. 5 of LSD[9-12] (Figure).

It may be pointed out that confirming the chemical conformation of a drug at its receptor site by clinical trial in humans is a relatively novel approach. In any event, knowledge of this apparent preferred conformation may now facilitate more direct studies of the psychedelic drug receptor in the brain.

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