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# LSD-25 ACTION IN NORMAL SUBJECTS TREATED WITH A MONOAMINE OXIDASE INHIBITOR*

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In 1954, Woolley and associates in this country and Gaddum and associates in Scotland dependently developed the concept that the central effects of LSD-25 may be due to an antagonism of serotonin in the brain (1, 2, 3). This was based on observations that LSD-25 is a potent antagonist of serotonin in vitro. Shortly thereafter, it was found that LSD-25 and serotonin are antagonists in vitro only when relatively high doses of LSD-25 are used. LSD-25, in small doses, may actually potentiate the effects of serotonin in vitro. As a result of these latter findings, several investigators have suggested that the psychotomimetic effects of LSD-25 may be due to a potentiation of serotonin action in the brain.

Several attempts have been made to test both of these hypotheses in man. Sjoerdsma et al. (4) administered LSD-25 to two patients whose blood serotonin levels were elevated as the result of malignant carcinoid. The psychological effects produced by LSD-25 in these patients were similar to those observed in normal subjects receiving LSD-25. Thus, high blood serotonin levels did not seem to alter the central effects of LSD-25. These results,

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however, may be explained on the basis that serotonin does not cross the blood-brain barrier in appreciable quantities. Consequently, the level of brain serotonin may not be elevated in these patients.

Several investigators have attempted to raise brain serotonin levels by pretreating normal subjects with 5 - hydroxytryptophan (5 - HTP), the precursor of serotonin, prior to the administration of LSD-25 to normal subjects. Experiments in animals have shown that 5 - HTP passes through the blood-brain barrier and is decarboxylated in the brain to form serotonin. Brengelmann et al. (5) and Pare et al. (6) pretreated normal subjects with 5-HTP and then administered a test dose of LSD-25. The results of both studies indicate that pretreatment with 5 - HTP appears to lessen slightly the effects of LSD-25. The moderating effects of 5 - HTP on LSD-25 were apparent statistically only in the Sympton Rating Scale and not in the Clyde Mood Scale nor in the clinical assessments. The subjects, when asked at the end of the experiment, could not distinguish between placebo plus LSD-25 and 5 -HTP plus LSD-25.

Klee et al. (7) also pretreated normal subjects with 5 -HTP followed by a test dose of LSD-25. These workers could not distinguish between the LSD-25-5-HTP and LSD-25 placebo combinations, except by the transient nausea produced by 5 - HTP. These investigators also studied the effects of pretreatment with "BAS" (l -benzyl - 2 - methyl - 5 - methoxytryptamine-hydrochloride), an anti-metabolite of serotonin, on LSD-25 action. "BAS" had no significant effect on the reactions of six normal males to LSD-25. These results were confirmed by Isbell et al. (8).

Thus, the concept of LSD-25-serotonin interaction has led to many attempts to raise brainstem serotonin in man, prior to a test dose of LSD-25. As already mentioned, this cannot be done very effectively by administering serotonin or its precursor, 5 -HTP, to man. Therefore, we attempted to accomplish this by pretreating normal subjects with a monoamine oxidase (MAO) inhibitor for several weeks prior to a test dose of LSD-25. In all animal

species studied; treatment with an MAO inhibitor results in increased levels of brainstem serotonin. In some species of animals, the levels of brainstem catecholamines are also raised, but not as much as that of serotonin.

## Methods and Results

Four normal, male adult volunteers drawn from the personnel of the Worcester Foundation for Experimental Biology participated in the study. The subjects were screened to ensure that none had a history of emotional upset. The LSD-25 for this study, kindly supplied by Sandoz Pharmaceuticals, Hanover, New Jersey, was d-lysergic acid diethylamide tartrate in sealed ampules containing O.1 mg per ml. All dosages referred to in this paper pertain to d-LSD-25 tartrate.

Each of the four subjects underwent six experimental situations:

(A) 40 mcg LSD-25 orally, with no premedication; after 2 weeks of treatment with isocarboxazide (Marplan), 30 mg a day; and after 5 weeks of treatment with Marplan, 30 mg a day.

(B) The above experimental situations were carried out using 75 mcg LSD-25, as the test dose.

The experiments were performed in a random fashion. Sufficient time was allowed between experiments to ensure recovery of the MAO enzyme system following prolonged treatment with Marplan. Successive daily doses of LSD-25 were never administered, thus obviating the possibility of the development of tolerance.

The following assessment criteria were used in evaluating the effects of LSD-25:

1. Autonomic responses
   a. Systolic and diastolic blood pressure
   b. Heart rate
   c. Pupillary size
2. Neurologic changes

The neurologic exam was directed toward evaluation of the sensory, motor, and autonomic systems, cerebellar functions, and the deep tendon and periosteal reflexes.

3. An ongoing evaluation of the mental state was also obtained by interview, behavioral observation, and the use of a sympton rating scale.

4. Objective psychological tests

We have chosen 2 assessments which have previously been found to change significantly under LSD-25 in normal subjects.

a. The Apparent Eye-Level Test

In this test, the subject is seated in a dark room and must adjust to apparent eye level a black line horizontally bisecting a square patch of light. The score taken reflects the position of apparent eye level in relation to objective eye level. Previous studies in normal males have shown that the apparent eye level shifts relatively upward after the oral ingestion of 40 and 75 mcg LSD-25. Under 125 mcg LSD-25, there is an initial rise followed by a drop in position of the apparent eye level with respect to placebo values. This suggests a biphasic action of LSD-25, which is dose-dependent.

b. The Stroop Color-Word Test - Card C

In this test, the subject is presented with a card containing 100 color-name words (red, green, blue) printed in an ink whose color is incongruent with the printed color-name. The subject's task is to name the color of ink in which the color-name words are printed (e.g., the word "blue" printed in green ink to which the subject must say "green" rather than "blue"). The score employed is the time taken to name the 100 ink colors on the card. This score is assumed to reflect the ability of a subject to maintain a designated task in the face of distraction. Under LSD-25, time taken to complete the test increases.

All of the assessments were carried out just before the oral ingestion of LSD-25 and at 1/2, 1, 2, 3, 4, and 5 hours after the ingestion of LSD-25.

The results of these preliminary experiments are as follows:

1. All four subjects volunteered the information that, following Marplan pretreatment, the experiences produced by LSD-25 were either very markedly attenuated or did not develop at all. This was confirmed by a symptom rating scale, and by interview and behavioral observations carried out by three investigators.

2. The objective psychological effects, the autonomic effects, and the neurologic responses to LSD-25 were also attenuated, and in some cases even reversed, following Marplan pretreatment.

3. All four subjects were emphatic in their convictions that, following LSD-25 plus Marplan pretreatment, they did not experience anything in any way similar to the experiences produced by LSD-25 without Marplan pretreatment.

## Discussion

If we assume that Marplan pretreatment in these subjects resulted in an elevation of brainstem serotonin, then we may conclude that the excess brainstem serotonin prevented LSD-25 from producing its psychologic effects-- either partially or completely. This may possibly be interpreted to mean that the psychological effects of LSD-25 are apparent in subjects with a normal brainstem serotonin. Raising brainstem serotonin by means of a MAO inhibitor does not allow for the development of the psychological effects of LSD-25. Since many investigators have claimed that active schizophrenics are relatively refractory to the psychologic effects of LSD-25, may we conclude that the brainstems of active schizophrenics contain an excess of indoleamines. Certainly direct evidence on this point is lacking. However, it is of interest to recall that several investigators have reported that labile schizophrenics in remission may become active schizophrenics when treated with MAO inhibitors (9), with MAO inhibitors plus reserpine (10, 11), with MAO inhibitors plus 5-HTP (12), and with MAO inhibitors plus tryptophan (13, 14). All of these drug treatments raise brainstem content of indoleamines. Thus, there is a possibility that active schizophrenics may have an excess of brainstem indoleamines. Under these conditions, LSD-25 may not be able to pro-

duce its effects since the brain indoleamine receptor sites may be partially or completely saturated.

Recent evidence seems to indicate that the MAO inhibitors and LSD-25 enhance the binding of serotonin in the particulate fraction of whole brain (15, 16). Perhaps pretreatment of our subjects with Marplan raised bound serotonin to a degree where LSD-25 could no longer exert any influence. Many more experiments will be necessary before the significance of LSD-25-serotonin interactions is elucidated.

Since LSD-25, in vitro, interacts with acetylcholine (Ach) in much the same way as it does with serotonin (17), LSD-25-Ach interactions may also play a significant role in producing the psychological effects of LSD-25. Similarly, Marplan may affect the metabolism of brain chemicals other than the indoleamines. In some species of animals, e.g., rat, mouse, rabbit, daily treatment with MAO inhibitors raises the levels of both brainstem indoleamines and catecholamines. In other species of animals, e.g., the cat, such treatment raises the levels of brainstem indoleamines without appreciably affecting the levels of brainstem catecholamines (18). Since adequate human studies are not yet available, it is not known whether pretreatment with Marplan raises the level of brainstem indoleamines alone or both indoleamines and catecholamines. In indirect experiments with Marplan, the evidence seems to indicate that brainstem indoleamines are raised after Marplan pretreatment without affecting appreciably the levels of the catecholamines (18). Direct evidence on this point, however, is lacking. Thus, it is conceivable that the results obtained in these experiments may be due to an increased level of brainstem catecholamines, as well as that of indoleamines. Finally, the antagonism of the psychologic effects of LSD-25 by Marplan may be due to an action of Marplan other than MAO inhibition.

## Summary

Four normal, male adult volunteers were given single oral doses of LSD-25 (40 mcg or 75 mcg) after treatment with isocarboxazide (Marplan), 30 mg a day, for 2 or 5 weeks. The

subjective experiences produced by LSD-25 were either very markedly attenuated or did not develop at all. This was confirmed by means of a symptom rating scale and by interview.

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