J. Psychiat. Res. Vol. 1, pp. 271—277. Pergamon Press Ltd. Printed in Great Britain

A FURTHER STUDY ON ALLEVIATION OF THE PSYCHOLOGICAL EFFECTS OF LSD IN MAN BY PRETREATMENT WITH 5-HYDROXYTRYPTOPHAN

C. M. B. PARE* and ELWOOD H. LABROSSE

Laboratory of Clinical Science, National Institute of Mental Health, U.S. Department of Health, Education and Welfare, Public Health Service, National Institutes of Health, Bethesda, Maryland.

(*Received* 18 *June*, 1962)
(*Revised* 31 *October*, 1962)

ON THE basis of the peripheral antagonism between lysergic acid diethylamide (LSD) and serotonin on smooth muscle, the concept arose that a similar central antagonism might account for the psychotomimetic properties of LSD.[1–3] Recently, BRENGELMANN *et al.*, [4] after studying the evidence for such a central antagonism, have obtained experimental evidence of their own which supported the hypothesis. These authors tested the hypothesis in man by using 5-hydroxytryptophan (5-HTP) in an effort to increase brain concentrations of serotonin. As predicted, the effects of LSD when preceded by 5-HTP were less than those following a similar injection preceded by saline. However, the moderating effects of 5-HTP were apparent only in the results of psychometric tests; with the dosage of 5-HTP used (25 mg), the after effects of the two LSD injections could not be distinguished on clinical observation. Only five subjects were used.

The present investigation was designed to repeat these experiments using higher doses of 5-HTP hoping that a clinically apparent alleviation of the LSD symptoms might be obtained.

METHOD

Drugs and dosage

In preliminary experiments, intravenous 5-HTP (DL) was given daily in increasing dosage to establish the maximum dose for each individual (Table 1). The occurrence of side effects was accepted provided these had completely subsided within 45 min after the injection of 5-HTP, or 15 min prior to the injection of LSD.

Similar experiments were done to establish the intravenous dose of LSD which would produce symptoms which could be quantified clinically, would leave the subject co-operative, able to carry out psychological tests, and willing to repeat the experience on subsequent occasions (see Table 1). The dose of LSD was considered adequate when it produced mild, but definite, perceptual disorders, in addition to the changes of mood which frequently occurred at lower dosages. These perceptual disorders were much more easily quantifiable than the changes of mood for assessing differences between experiments. These preliminary

* Present address: Department of Psychiatry, St. Bartholomew's Hospital, London, E.C.1, England.

TABLE 1. RATING SCALE SCORES AFTER PRETREATMENT WITH 5-HYDROXYTRYPTOPHAN (5-HTP) AND SALINE AND AFTER INTRAVENOUS LYSERGIC ACID DIETHYLAMIDE

Subject No.	5-HTP Dosage	After Saline or 5-HTP: 0		½ hr		1 hr		LSD Dosage	Time after LSD Injection: ½ hr		1 hr		2 hr		3½ hr	
		S[1]	H[2]	S[1]	H[2]	S[1]	H[2]		S[1]	H[2]	S[1]	H[2]	S[1]	H[2]	S[1]	H[2]
1*	40 mg	5	3	4	17			40 μg	29	13						
2*	25 mg	2	2	3	13			30 μg	20	19						
3*	40 mg	4	5	4	7		6	50 μg	5	7	12	7	38	11	40	9
4*	40 mg	0	1	0	5	0		50 μg	14	5	21	5	61	18	21	6
5	35 mg	3	4	4	10	4	4	40 μg	21	15	25	35	17	57	12	18
6*	45 mg	3	3	3	7	3	3	50 μg	52	40	60	57	74	58	62	44
7	35 mg	3	3	3	9	3	3	40 μg	29	28	45	37	36	21	30	28
8	30 mg	0	2	2	3	1	5	40 μg	10	17	16	37	42	21	13	28
9*	45 mg	1	2	5	7	4	4	50 μg	42	26	44	30	36	25	23	16
10	60 mg	3	3	1	5	2	4	60 μg	27	29	55	55	68	66	71	73
11*	60 mg	2	1	1	1	2	2	60 μg	40	19	58	30	46	37	38	19
12*	55 mg	0	0	1	2	0	6	50 μg	16	4	18	10	22	12	17	9
13*	55 mg	3	1	1	6	2	0	55 μg	46	27	94	72	62	74	61	50
Mean ± S.D.																
Saline Pretreatment:		2 ± 2		2 ± 2		2 ± 2			27 ± 15†		41 ± 25		46 ± 19		35 ± 21	
5-HTP Pretreatment:		2 ± 1		7 ± 4		3 ± 2			19 ± 11†		34 ± 21		36 ± 23		27 ± 20	

[1] Rating Scale scores obtained at the designated periods when saline was the pretreatment.
[2] Rating Scale scores obtained at the designated periods when 5-hydroxytryptophan was the pretreatment.
* In these subjects the clinical prediction of the date of 5-HTP administration was correct.
† This difference is statistically significant at $P<0{\cdot}02$.

experiments, by affording the subjects an LSD experience and familiarizing them with the psychological tests (see below), allowed subsequent experiments to be more comparable. To avoid tolerance effects, these preliminary studies were always done at least one week before the experiment proper.

Subjects

Seventeen healthy volunteers between the ages of 18–25 years, were given a rigorous physical and psychiatric examination prior to the experiment. Of these, four had to be rejected because they developed gastrointestinal symptoms at a low dosage of 5-HTP. Of the remaining 13 subjects, 9 were female.

Design

After preliminary experiments to establish optimal doses of 5-HTP and LSD, each subject was given an intravenous injection of saline or of 5-HTP, followed in one hour by an intravenous injection of LSD. One week later, at the same time of the day, the subject was given an intravenous injection of the alternative pretreatment followed in one hour by LSD. The order of saline or 5-HTP injection on the first week was randomized for each individual by the toss of a coin. In the case of 8 subjects the order of injections was saline preceding the LSD on the first occasion, and in the case of 5 subjects the 5-HTP was given on the first occasion. Neither the subjects nor the assessing investigator were informed as to the occasion on which 5-HTP was administered. Several times the occurrence of nausea and vomiting served as strong clues to the subjects as to when they had received 5-HTP, but the accuracy of these guesses by the subject was not made known to them during the study. Both the subjects and the assessing investigator were informed that LSD was given at each experimental period.

Assessment of symptoms

The assessor was admitted to the test room just prior to the injection of LSD and only when side effects, if any, of 5-HTP had completely subsided. Assessment of symptoms was made in three ways: 1, Clinically, i.e. by interview and behavioral observation; 2, by a four point rating scale[5] previously shown to be a valid test of LSD symptoms, [6] and 3, by a self-administered mood scale.[7] The assessment was carried out at one-half, one, two, and three and one-half hours after the LSD injection. When the experiment on each individual was completed, and before scoring the rating scale, the assessor made a clinical judgement as to which week the subject had been given 5-HTP. The mood scale was scored mechanically using the IBM 650 computer.[8]

RESULTS

1. 5-HTP regularly resulted in mild gastrointestinal symptoms and occasionally a slight fall of blood pressure. In no case did these symptoms persist from more than 20–30 min and in every case the symptoms had subsided 15 min prior to the LSD injection. In addition to these frequently described side effects, one patient repeatedly felt drowsy and yawned following 5-HTP administration.

In Table 1 the scores for the Symptom Rating Scale are shown; the more marked the

symptoms, the higher the score. During the one hour period after the initial injection, but before LSD, it can be seen that the mean scores are significantly lower than after LSD and it is particularly of interest that there is no significant difference between the mean scores after the saline and 5-HTP pretreatments at the period just prior to LSD administration (saline = 2·1 ±1·5, 5-HTP = 3·1 ±2·0; mean ± S.D.).

2. Effect of 5-HTP on LSD. Acting on the assumption that 5-HTP reduces LSD symptoms, the assessor was required to make a definite prediction in each case, as to the occasion on which 5-HTP had been given. He was correct in the case of 9 subjects and wrong in four (Table 1); the accuracy of this clinical assessment is not statistically significant.

The mean results on the rating scale showed fewer LSD symptoms on the occasions when the subjects were pretreated with 5-HTP, as compared to saline pretreatment, at each of the test periods. For eleven subjects, numbers 3 through 13 (Table 1) the test data are relatively complete; 6 of these subjects received saline on the first occasion and 5 subjects received 5-HTP on the first occasion. When analyzed statistically using a cross-over design, no order effect was found at any of the test periods. However, the drug effect, i.e. pretreatment effect as measured by this rating scale, was statistically significant at the ½ hr test period ($F = 2{\cdot}83$, $p<0{\cdot}02$), but not statistically significant at the later time periods. The rating scale scores at ½, 1, 2, and 3½ hr after LSD for the occasions when 5-HTP was the pretreatment was subtracted from the scores for the corresponding periods for the occasions when saline was the pretreatment. These differences in the scores were found to be significantly correlated ($P = 0{\cdot}05$) with the dose of 5-HTP at the ½ hr test period ($r = +0{\cdot}58$) and at the 1 hr test period ($r = +0{\cdot}62$).

Although the mood scale showed a distinct change after LSD, it revealed no difference between the occasions when 5-HTP was given and when saline was given as the pretreatment (Table 2).

DISCUSSION

KLEE *et al.*[9] also have attempted to alleviate the psychological effects of LSD with 5-HTP but found no effect. Following the administration of 5-HTP by slow intravenous drip, they gave the LSD orally and assessed the subjects' mental state three to five times on each experimental day and again the following day. Klee's negative findings might be explained by: 1, insufficient sensitivity and precision of the clinical evaluation, as found in our study, 2, low dose rate of the intravenous administration of 5-HTP (1·11 mg/min in the case of one subject; no details were given regarding the others), or 3, other difficulty in timing of the observations so that they did not correspond to the peak period of LSD effect.

In our study the 5-HTP was administered intravenously over about 10 sec; this method of administration can be expected to produce maximal gastrointestinal and other symptoms within 15 to 20 min followed by a decrease. In agreement with the report of DAVIDSON *et al.*,[10] we found that lengthening the period of infusion up to 30 min did not eliminate the gastrointestinal symptoms. Therefore, we used the 10 sec infusion period so that the gastrointestinal symptoms would be gone before the LSD was administered. The effect of 5-HTP or saline pretreatment on the symptoms arising after LSD is statistically significant ($P<0{\cdot}025$) only at the half-hour period after LSD. At this period the LSD symptoms are fewer and therefore the percentage difference is greater. In addition, the variance is much

TABLE 2. MEAN RATINGS* OF FACTORS FROM THE CLYDE MOOD SCALE ON 11 NORMAL SUBJECTS PRETREATED WITH 5-HTP OR SALINE FOLLOWED BY LSD

CMS Factors	Pretreatment	Test Periods 1	2	3	4	5
Friendly	5-HTP	47·5	39·3	38·8	36·9	35·5
	Saline	47·0	44·0	39·0	40·8	43·2
Energetic	5-HTP	49·8	41·0	38·1	39·0	37·6
	Saline	50·5	47·2	34·2	41·4	43·7
Clearthinking	5-HTP	51·1	47·6	37·1	35·1	36·8
	Saline	52·0	50·6	35·8	36·1	42·5
Aggressive	5-HTP	41·2	39·0	43·4	44·5	45·8
	Saline	41·8	40·5	42·5	47·4	46·5
Jittery	5-HTP	44·9	44·1	56·4	59·2	57·6
	Saline	47·3	43·4	59·1	61·8	55·0
Depressed	5-HTP	40·1	42·3	45·8	49·0	48·8
	Saline	40·6	41·6	47·4	47·7	46·5

* The data in this table are standard scores (5a). The test period 1 preceded any treatment, test 2 was administered 1½ hr after saline or 5-hydroxytryptophan (5-HTP) injection and periods 3, 4 and 5 were 1½ hr, 2 hr, and 3½ hr after LSD injection.

less, the smaller variance ($S^2 = 323$) is the factor which makes the difference of 7·9 statistically significant at the half-hour period while the larger difference of 9·2 at the two hour period is not statistically significant because of the larger variance ($S^2 = 881$) of the scores at this period.

UDENFRIEND *et al.*[11] have reported on the changes in serotonin content of rat brains following iproniazid (75 mg/kg) and 5-hydroxytryptophan (100 mg/kg). In contrast to their findings, we would expect smaller elevations of serotonin in brain, and an earlier onset of decline, in view of the instantaneous administration and much lower doses (0·4 to 0·9 mg/kg) used on the subjects in our study. On the basis of these considerations, the brain levels of serotonin would be expected to be decreasing during the later test periods after LSD; this suggests an explanation as to why pretreatment does not show a statistically significant influence on the LSD effect at the later periods.

The present investigation closely followed the methods used by BRENGELMANN *et al.*[4] and the results are in agreement, i.e. the results of the symptoms rating scale were more reliable than clinical assessment in evaluating the pretreatment effect of 5-HTP on the symptoms produced by LSD.

The finding of a statistically significant correlation between the 5-HTP dose and the difference between the scores ("5-HTP pretreatment" minus "saline pretreatment") on the rating scale at the ½ and 1 hr periods, also lends support to the hypothesis that 5-HTP pretreatment lessens the effect of LSD. In addition, the accuracy of the clinical assessment is related to dose; at 40 mg of 5-HTP there were 8 correct assessments out of 9 trials; while at less than 40 mg only one was correct out of 4.

In contrast to the findings with the Symptom Rating Scale, the Clyde Mood Scale, though demonstrating a response to LSD, revealed no significant differences between the occasions when LSD was preceded by 5-HTP or saline. A possible explanation for the discrepancy between these two psychological tests may be that the Symptom Rating Scale is more specific for drug effects while the Clyde Mood Scale measures more general changes in affect.

The results obtained by BRENGELMANN *et al.*[4] and in this study in which 5-HTP pretreatment appears to lessen the effect of LSD, may be explained at least two ways. First, these results may suggest a direct antagonism between 5-HTP (or its product, serotonin), and LSD in the brain; this explanation has been advanced earlier by others, as mentioned above.[1–4] Secondly, it is well known that sedatives such as sodium amytal lessen the psychological effects of LSD. Although such a sedative action was not discernible in Brengelmann's tests, one of our subjects repeatedly became drowsy and yawned following 5-HTP. Such a nonspecific effect of 5-HTP on LSD cannot be excluded.

In conclusion, the results of this study provided further evidence that 5-hydroxytryptophan pretreatment reduces LSD symptoms in man, which it may do by increasing brain serotonin. This finding lends further support to the hypothesis that LSD produces psychotomimetic effects in man by a central antagonism to serotonin.

SUMMARY

In this study of the possible alleviation of LSD symptoms by pretreatment with 5-hydroxytryptophan (5-HTP), the dose of 5-HTP was increased to a maximum under the experimental conditions. Nine female and four male subjects were given an intravenous injection of 25 to 60 mg of DL-5-HTP or 0·9 per cent saline solution followed, in one hour, by 30 to 60μg of lysergic acid diethylamide (LSD). The pretreatment was given in a double-blind design. Clinical assessment of the occasion on which 5-HTP was the pretreatment was correct in 9 cases (not statistically significant). The Symptoms Rating Scale was administered before, $\frac{1}{2}$ hr, and 1 hr after the pretreatment, and $\frac{1}{2}$, 1, 2, and $3\frac{1}{2}$ hr after LSD. The results obtained on this scale showed significantly ($P<0{\cdot}02$) fewer symptoms $\frac{1}{2}$ hr after LSD on the occasion when 5-HTP was the pretreatment. The results on the Clyde Mood Scale showed an LSD effect, but no significant effect of pretreatment.

The findings of this study are in agreement with an earlier study and strengthen the conclusion that pretreatment with 5-hydroxytryptophan decreases the symptoms produced by lysergic acid diethylamide. The mechanism of this action is not yet clear; it may possibly be due to an increase of serotonin in the brain as a result of the administration of its precursor, 5-hydroxytryptophan.

Acknowledgements — We wish to express our sincere appreciation to the nurses on Ward 4-West who gave invaluable assistance during this study, and to Drs. Seymour Geisser and Donald F. Morrison for their help with the statistical analyses.

REFERENCES

1. GADDUM, J. H. Antagonism between lysergic acid diethylamide and 5-hydroxytryptamine. *J. Physiol.*, **121,** 15, 1953.
2. AMIN, A. H., CRAWFORD, T. B. B. and GADDUM, J. H. The distribution of substance P and 5-hydroxytryptamine in the central nervous system of the dog. *J. Physiol.*, **126,** 596, 1954.
3. WOOLLEY, D. W. and SHAW, E. A biochemical and pharmacological suggestion about certain mental disorders. *Science*, **119,** 587, 1954.
4. BRENGELMANN, J. C., PARE, C. M. B. and SANDLER, M. Alleviation of the psychological effects of LSD in man by 5-hydroxytryptophan. *J. ment. Sci.*, **104,** 1237, 1958.
5. ABRAMSON, H. A., JARVIK, M. E., KAUFMAN, M. R., KORNETSKY, C., LEVINE, A. and WAGNER, M. Lysergic acid diethylamide (LSD-25): I. Physiological and perceptual responses. *J. Psychol.* **39,** 3, 1955.
6. BRENGELMANN, J. C. Effects of LSD-25 on test of personality. *J. ment. Sci.*, **104,** 1226, 1958.
7. CLYDE, D. Self ratings. In *Drugs and Behavior*, UHR, L. and MILLER, J. G. (Editors), pp. 583–586. John Wiley and Sons, New York, 1960.
8. CLYDE, D. J. *Clyde Mood Scale: Explanation of scoring key No. 2, Sept. 1959*, Biometric Laboratory, George Washington University, Washington 6, D.C.
9. KLEE, G. D., BERTINO, J., CALLAWAY, E. and WEINTRAUB, W. Clinical studies with LSD-25 and two substances related to serotonin. *J. ment. Sci.*, **106,** 301, 1960.
10. DAVIDSON, J., SJOERDSMA, A., LOOMIS, L. N. and UDENFRIEND, S. Studies with the serotonin precursor, 5-hydroxytryptophan. *J. Clin. Invest.*, **36,** 1594, 1957.
11. UDENFRIEND, S., WEISSBACH, H. and BOGDANSKI, D. F. Increase in tissue serotonin in following administration of its precursor 5-hydroxytryptophan. *J. biol. Chem.*, **244,** 803, 1957.