EFFECTS OF 5-HYDROXYTRYPTOPHAN ON SCHIZOPHRENIA

By

J. C. BRENGELMANN, M.D., Ph.D.

Research Assistant

Institute of Psychiatry, Maudsley Hospital, London, S.E.5

C. M. B. PARE, M.D.(Camb.), M.R.C.P., D.P.M.

Senior Registrar

Bethlem Royal and the Maudsley Hospital, London, S.E.5

and

M. SANDLER, M.B.(Manch.), M.R.C.P.*

Lecturer in Chemical Pathology

Royal Free Hospital, London, W.C.1

INTRODUCTION

THE present investigation represents a logical continuation of a previous experiment where it was shown that the injection of 5-hydroxytryptophan (5HTP) alleviates the psychological effects of lysergic acid diethylamide (LSD-25) (Brengelmann, Pare and Sandler, 1958). LSD is of interest in psychiatry because the psychotomimetic effects of the drug bear a resemblance to schizophrenia clinically, in psychological tests and, according to Hoagland, Rinkel and Hyde (1955), in their abnormal excretion of urinary phosphate. The possibility presents itself that, in some cases of schizophrenia, the functional abnormality is similar to that produced by LSD.

Gaddum (1953b) noted that LSD was an effective antagonist to the action of 5-hydroxytryptamine (5HT) on the peripheral tryptamine receptors of smooth muscle (Gaddum, 1953a). From this arose the concept that a central antagonism to 5HT might account for the psychological properties of LSD (Amin, Crawford and Gaddum, 1954). Evidence supporting this suggestion has recently been put forward by Brengelmann, Pare and Sandler (1958). These authors showed that the psychological effects of LSD were reduced by increasing the brain concentrations of 5HT. This was done by giving the precursor substance 5HTP which, unlike 5HT, readily passes the blood brain barrier to be decarboxylated *in situ* to 5HT.

Woolley and Shaw (1954) suggested that schizophrenia may be caused by some naturally occurring LSD-like substance. If this is so, then the psychosis in these patients should also be relieved by 5HTP. This is the major hypothesis of the present investigation.

Any future work of a related kind may come up against the complication that only a certain type of patient benefits from a particular kind of treatment whereas others remain refractory. While the number of subjects used in the present investigation is obviously too small to study this point conclusively, a suggestive result may well provide a useful pointer for future research. For this

* Now at Queen Charlotte's Maternity Hospital, London, W.6.

https://doi.org/10.1192/bjp.105.440.770 Published online by Cambridge University Press

reason, personality questionnaires of rigidity, extraversion and neuroticism were administered to the patients. It is known from previous (Brengelmann, 1958a, 1959), as well as from more recent unpublished results, that schizophrenia and questionnaire rigidity vary significantly in a similar manner when correlated with a number of objective test scores. The same experiments have, furthermore, shown that adaptation to external stimuli in terms of various learning and perceptual scores is lowest for schizophrenics and rigid subjects. From this, it may be inferred that if 5HTP does benefit schizophrenic patients, highly rigid schizophrenics will benefit less than those low in rigidity. No such relationship is expected for extraversion and neuroticism.

Method

1. *General Procedure*

Eleven patients aged 18–65 years (mean 32 years) were selected because of the confidence in the diagnosis of schizophrenia, the acute phase of their illness and the fact that they were receiving no specific treatment. There were six male and five female subjects. Early morning specimens of urine were collected prior to the investigation proper from six of the eleven patients. Two-dimensional indole chromatograms and estimation of 5-hydroxyindoleacetic acid in mg./g. creatinine were done by methods described elsewhere (Brengelmann, Pare and Sandler, 1958).

Following a battery of psychological tests, the subject was given an intravenous injection of 25 mg. DL-5HTP in 5 ml. solution, or an equivalent amount of placebo. Two hours later the psychological tests were again administered. At the same time next day the investigation was repeated alternating the 5HTP and placebo.

2. *Psychological Apparatus Tests*

The psychological tests used have been described in a previous publication (Brengelmann, 1958b). The scores are briefly re-stated as follows.

Perceptual Reaction Test (PRT): degree of variability. In contrast to the previous single administration the PRT was now given three times on each occasion in order to increase reliability. The score was mean degree of variability, as before. This score was, however, computed as variability between the three administrations instead of between initial practice and subsequent occasions.

After-image Duration: duration of the negative after-image of a red square.

Rotation Error (FRT): error in reproducing the position of visually exposed stimuli (immediate recall).

Positive or Subjective Recognition (FRT): number of patterns "subjectively" recognized out of a total of 30, ten of which having been shown previously.

Size Variability (FRT): variability in the size of stimuli reproduced by drawing (expressive movement).

The first four scores are known to discriminate clearly between schizophrenics on the one hand and normals and neurotics on the other. Scores increased or decreased in the order: normals—neurotics—schizophrenics. The fifth score (size variability) discriminated as with the above pattern though not to a high degree. This score was mainly included because of the clear results it has yielded with regard to the effect of 5HTP on LSD effects (Brengelmann, Pare and Sandler, 1958).

https://doi.org/10.1192/bjp.105.440.770 Published online by Cambridge University Press

3. *Personality Questionnaires*

The extraversion and neuroticism questionnaires used are those developed by Eysenck (1956). As a result of an item analysis, the rigidity questionnaire comprised the following items of a previously published scale (Brengelmann, 1959): 1, 3, 6, 7, 8, 9, 11, 13, 16, 17, 19, 20, 27 and 28. With 14 items, the range of scores is from 0 to 28, weights being 2 for each response in the rigid direction and 1 for an undecided response (question mark).

4. *Design and Predictions*

The order of tests was constant for all five occasions as follows: after-image, PRT I, rotation error I, subjective or positive recognition I, PRT II, rotation error II, subjective recognition II, PRT III. Testing lasted about one hour on each occasion. The following basic design was employed:

practice—control 1—post-injection 1—control 2—post-injection 2.

Placebo and 5HTP were assigned to injections 1 and 2 in a randomly balanced manner. The psychologist did not know which injection had been given.

If 5HTP acts to reduce schizophrenic effects towards normality, the following predictions must be made.

Predictions for Test Scores	*5HTP Score as Against Placebo or Control Conditions*
1. PRT degree of variability	lower
2. After-image duration	higher
3. Rotation error	lower
4. Positive or subjective recognition	lower
5. Size variability	lower

Results

1. *Objective Test Results*

Before discussing the results, a comparison is made between the present schizophrenic responses and the corresponding previous responses of normals (Brengelmann, 1958) in order to demonstrate the validity of the tests used in the present study. The schizophrenic scores deviated in the expected direction for all tests. With the exception of size variability, which has already been stated to be a relatively poor discriminator, the differences were considerable, as may be seen from a comparison between the present results (Fig. 1) and those obtained in the investigations already quoted.

The group means are shown in Figure 1. Some previous score norms are provided in dotted lines.

A comparison between the predictions made and Figure 1 reveals that the group trends of four of the five test scores (PRT, after-image, rotation error and recognition) contradict the expectation. Only size variability conforms with the prediction.

The directions of the individual responses are shown in Table I. Two comparisons are made over all 55 responses to the five tests. Firstly, 5HTP and placebo are compared with their own control tests. Secondly, 5HTP responses are assessed directly against placebo instead of its own control, thus using the placebo scores as a baseline. By this method, the number of events confirming or rejecting the hypothesis is then tested against the theoretically expected

https://doi.org/10.1192/bjp.105.440.770 Published online by Cambridge University Press

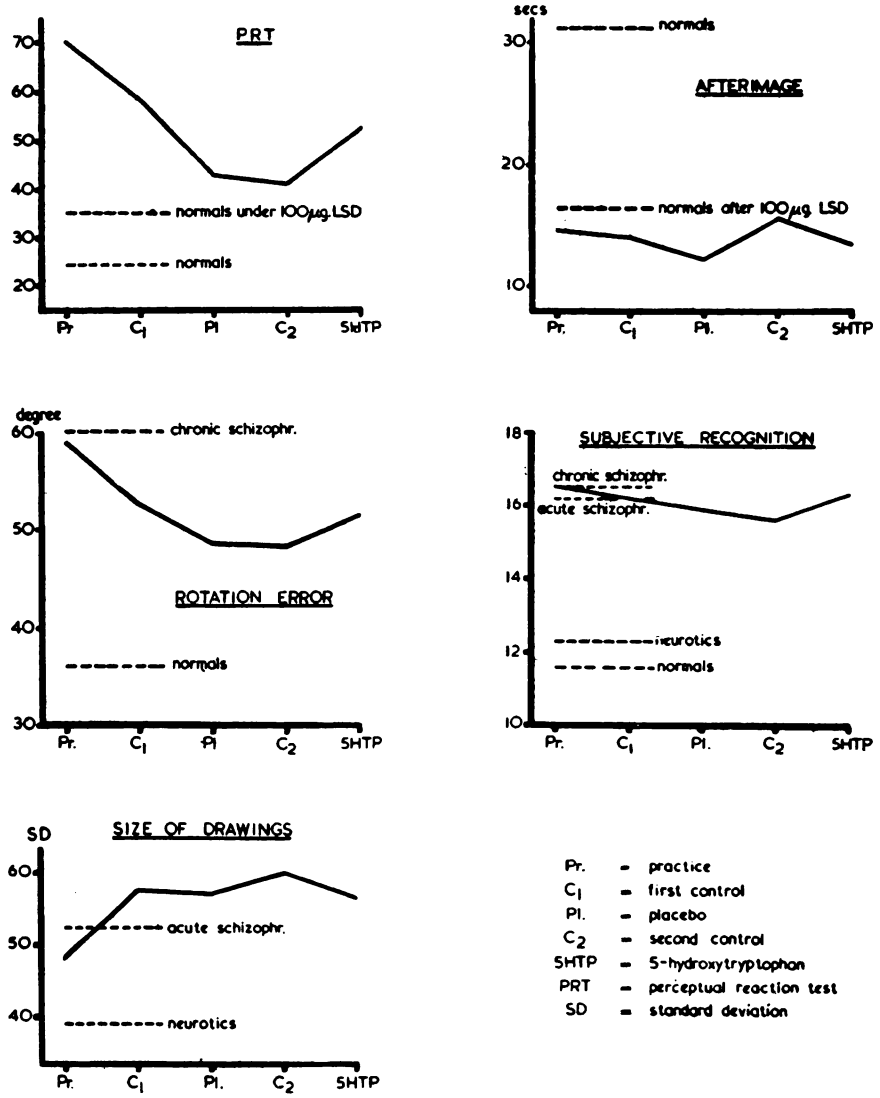


FIG. 1.—Group means of eleven acute schizophrenic patients.

frequency of 27·5 (half the total number of 55 responses). Most of the discussion is based on the latter comparison.

The first comparison shows that 25 of the 55 5HTP responses contradict the hypothesis. For placebo, 32 responses accord with the prediction made for 5HTP, suggesting that placebo was more beneficial than 5HTP. Testing the 5HTP results against placebo, a chi-square of 3·661 (1 d.f.) is obtained which is not significant at the 5 per cent. level.

As to the second comparison, 23 5HTP responses confirm the prediction, whereas 32 are contradictory. A test of these observed frequencies against the theoretically expected frequencies results in a chi-square of 1·472 (1 d.f.) which is not significant.

https://doi.org/10.1192/bjp.105.440.770 Published online by Cambridge University Press

TABLE I

Direction of Individual Test Responses with Regard to Predictions

		5HTP vs. Own Control (Placebo vs. Own Control)					5HTP vs. Placebo					5HIAA
	Tests	1	2	3	4	5	1	2	3	4	5	
Subjects	1 ..	+ (+)	+ (+)	− (+)	− (+)	+ (+)	+	−	−	+	−	
	2 ..	+ (+)	+ (−)	+ (+)	− (+)	− (−)	−	+	−	−	−	
	3 ..	+ (−)	− (+)	− (−)	+ (−)	− (+)	+	+	+	+	−	
	4 ..	− (+)	− (−)	+ (+)	− (−)	+ (−)	−	−	−	−	+	3·3
	5 ..	+ (+)	+ (−)	− (+)	− (+)	− (−)	+	+	−	−	−	1·6
	6 ..	+ (−)	− (−)	+ (−)	− (+)	+ (−)	+	−	+	−	+	1·6
	7 ..	− (+)	− (+)	− (+)	+ (−)	− (+)	−	+	−	+	−	
	8 ..	+ (−)	− (−)	− (+)	+ (+)	− (+)	+	−	−	+	−	1·3
	9 ..	+ (+)	+ (+)	+ (+)	− (−)	− (−)	+	+	−	−	−	3·1
	10 ..	− (+)	− (+)	− (+)	+ (+)	− (+)	−	−	−	+	−	
	11 ..	− (−)	+ (−)	− (−)	+ (+)	+ (−)	−	+	−	+	+	2·8

+ = score is reduced in normal direction.
− = score remains the same or is increased in the schizophrenic direction.
Values for 5-hydroxyindoleacetic acid (5HIAA) in early morning specimens of urine are expressed as mg./g. creatinine.

2. *Questionnaire Results*

Subject 7 refused to complete the questionnaires. Results obtained for all other subjects are shown in Table II.

TABLE II

Questionnaire Scores of Rigidity, Extraversion and Neuroticism

Subjects	Rigidity (R)	Extraversion (E)	Neuroticism (N)
1	26	10	8
2	16	14	34
3	14	19	27
4	26	28	36
5	18	15	22
6	10	20	10
8	8	27	20
9	14	17	38
10	20	32	17
11	6	30	27

Dividing the ten subjects into the five most rigid and five least rigid patients, the following relationship to the effect of 5HTP on test performance (compare 5HTP/placebo section in Table I) is obtained (Table III).

TABLE III

Rigidity Interacts Significantly with the Effect of 5HTP on Test Performance of Schizophrenics. "Prediction" Refers to the 5HTP/Placebo Comparison Shown in Table I

	Low R	High R	E	I	Low N	High N
For prediction	14	7	10	11	10	11
Against prediction ..	11	18	15	14	15	14
Chi-square	4·024		0·082		0·082	
Significance (1 d.f.) ..	5%		N.S.		N.S.	

Of the 25 predictions pertaining to the five most rigid subjects, 18 are found to vary against and 7 in favour of the main hypothesis, that 5HTP reduces test responses towards normality. The corresponding figures for the low rigidity sub-group are 14 for and 11 against the hypothesis. This relationship is significant at the 5 per cent. level (2·5 per cent. for a one-tail test) as expressed by a chi-square test of independence. The corresponding relationships for extraversion and neuroticism are clearly insignificant. This result confirms the prediction that rigidity interacts significantly with the effects of 5HTP on the test performance of schizophrenics.

https://doi.org/10.1192/bjp.105.440.770 Published online by Cambridge University Press

3. *Sex*

Patients 1, 4, 5, 9 and 10 were of female, the rest of male sex. An inspection of Table I (5HTP/placebo portion) shows that of the 25 predictions for the five female patients eight were for and seventeen against the prediction. The corresponding figures for the six males were each fifteen for and against. This relationship is not significant (chi-square+1·809, 1 d.f.).

4. *Biochemical Results*

Using patients numbered 4, 5, 6, 8, 9 and 11, an attempt was made to correlate the effect of 5HTP on the psychological test scores on the one hand, with the urinary excretion of 5HIAA and the pattern of the urinary indole chromatogram on the other (Table I). No systematic relationship was found between the biochemical and psychological findings.

5. *Conclusions*

The hypothesis that 5HTP will alter the psychological scores of schizophrenics as an unselected group in the direction of normality has not been confirmed. The results obtained contradict the hypothesis but not significantly so. The suggestion is made that this effect of 5HTP on performance may be significantly dependent on the personality trait of rigidity as defined by the questionnaire method.

Discussion

The results of the present investigation must be interpreted in the light of the authors' previous paper, where a marked alleviation of some psychological effects of LSD in normals by 5HTP was found. In the present investigation on schizophrenia, where the investigators, the environment and the experimental method were similar, the overall results showed, if anything, a slight worsening of the psychological abnormalities. This is in conformity with the experience of Hoagland (1958) who gave daily doses of 100 mg. 5HTP to schizophrenics for two weeks without noticing any improvement in their mental state.

The significant interaction obtained between personality rigidity and the effect of 5HTP on test performance may be of importance though apparently not with regard to the expected benefit of 5HTP injection. As Table III indicates, the main contribution to the significance of the result is on the negative side of the prediction. In other words, it may be suggested that the combination of high rigidity and 5HTP injection leads to a deterioration of performance whereas low rigid patients are little effected by the injection. This formulation does not consider the beneficial effect of 5HTP but simply relates to unspecific drug effects.

Leyton (1958) has suggested that a group of schizophrenics may be identified by their low urinary excretion of 5HIAA and that this group of patients benefits from the injection of 5HTP. In six subjects so tested there was no suggestion that patients with a low urinary excretion of 5HIAA responded to 5HTP any better than those with a higher rate of excretion. Though the number of patients is too small to warrant any suggestion, it should be noted that the results did not support Leyton's hypothesis.

Finally, it may be stated that the suggestion made by Woolley and Shaw (1954) that schizophrenia may be caused by some naturally occurring LSD-like substance has not been confirmed.

https://doi.org/10.1192/bjp.105.440.770 Published online by Cambridge University Press

SUMMARY

The hypothesis was tested that excess of brain 5-hydroxytryptamine (5HT), as produced by the injection of 5-hydroxytryptophan (5HTP), leads to a reduction of psychotic test effects in schizophrenics. The perceptual and memory tests used had previously been validated on abnormals and in LSD research with normals. The hypothesis was not confirmed.

ACKNOWLEDGMENTS

We wish to thank Miss Lilith Emslie and Miss Doreen Crabtree of the Royal Free Hospital for skilled technical assistance, and the Royal Free Hospital Endowment Fund and Roche Products Ltd., for defraying their respective salaries. Roche Products Ltd., also provided supplies of 5-hydroxytryptophan.

REFERENCES

1. 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.*, 1954, **126**, 596–618.
2. BRENGELMANN, J. C., "The effects of exposure time in immediate recall on abnormal and questionnaire criteria of personality", *J. Ment. Sci.*, 1958a, **104**, 665–680.
3. *Idem*, "Effects of LSD-25 on tests of personality", *ibid.*, 1958b, **104**, 1226–1236.
4. *Idem*, "Abnormal and personality correlates of certainty", *ibid.*, 1959, **105**, 142–162.
5. *Idem*, PARE, C. M. B., and SANDLER, M., "Alleviation of the psychological effects of LSD in man by 5-hydroxytryptophan", *ibid.*, 1958, **104**, 1237–1244.
6. EYSENCK, H. J., "The questionnaire measurement of extraversion and neuroticism", *Riv. psychol.*, 1956, **50**, 113–140.
7. GADDUM, J. H., "Tryptamine receptors", *J. Physiol.*, 1953a, **119**, 363–368.
8. *Idem*, "Antagonism between lysergic acid diethylamide and 5-hydroxytryptamine", *ibid.*, 1953b, **121**, 15.
9. HOAGLAND, H., "Biochemical aspects of schizophrenia", *J. nerv. ment. Dis.*, 1958, **126**, 211.
10. *Idem*, RINKEL, M., and HYDE, R. W., "Adrenocortical function and urinary phosphate excretion; comparison in schizophrenia and in lysergic acid diethylamide-induced psychotic episodes in normal persons", *A.M.A. Arch. Neurol. Psychiat.*, 1955, **73**, 100–109.
11. LEYTON, G. B., "Indolic compounds in the urine of schizophrenics", *Brit. Med. J.*, 1958, *ii*, 1136.
12. WOOLLEY, D. W., and SHAW, E., "Some neurophysiological aspects of serotonin", *ibid.*, 1954, *ii*, 122–126.

https://doi.org/10.1192/bjp.105.440.770 Published online by Cambridge University Press