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On the Relationship of Serotonin to Schizophrenia

In 1954, Woolley and Shaw (*1*) formulated the working hypothesis that a cerebral serotonin deficiency or serotonin excess might be a cause of mental disturbances such as those characteristic of schizophrenia. The evidence available at that time which suggested that serotonin played a vital part in the functioning of the central nervous system was of a twofold nature: (i) serotonin occurs in the brain, especially in the hypothalamus (*2, 3*), and (ii) some drugs which act as antimetabolites of serotonin on smooth muscle preparations also cause mental aberrations (*4*). This is especially true of the powerful psychotomimetic agent lysergic acid diethylamide (LSD). Additional evidence has since been presented by Woolley (*5*). Further, Sano (*6*) has reported that the administration of reserpine to psychotic patients causes a temporary increase in urinary 5-hydroxyindoleacetic acid (5-HIAA).

Whether serotonin is involved in the etiology of schizophrenia might be decided by establishing whether serotonin metabolism differs in nonpsychotic well subjects and in schizophrenic patients. We therefore investigated the urinary excretion of its principal metabolite, 5-HIAA, in both groups (*7*). Untreated male chronic schizophrenic patients (median age, 42 years; range, 24 to 63) were selected from the research wards of the Worcester State Hospital and maintained on the normal hospital diet. Acutely ill male schizophrenic patients (median age, 33 years; range, 16 to 57) were selected from the admission wards, and urine samples were obtained before therapy was instituted. All urine samples were collected in the morning and analyzed by the Udenfriend colorimetric procedure for 5-HIAA (*8*). The results are shown in Table 1. Statistical analysis shows that there is no significant difference in the excretion of 5-HIAA between chronic or acute schizophrenic patients and nonpsychotic well subjects. These findings agree with those of others (*6, 9*). The output of 5-HIAA in normal subjects ranged from 0.7 to 13.2 mg/day and in schizophrenic patients from 0.3 to 31.6 mg/day. Bellak (*10*) has commented on the greater variability of values for almost any factor investigated.

Table 1. Urinary excretion of 5-hydroxyindoleacetic acid in male subjects. S.E., standard error.

Diagnosis	Subjects (No.)	Output of 5-HIAA (μg/ml) ± S.E.	Output of 5-HIAA (mg/day) ± S.E.
Chronic schizophrenia*	30†	4.7 ± 0.4	5.3 ± 0.4
Paranoid	7	4.6	4.3
Catatonic	3	3.3	5.5
Hebephrenic	5	3.6	6.2
Simple	3	6.9	6.2
Undifferentiated	12	4.9	5.4
Acute schizophrenia	23†	4.7 ± 0.6	5.5 ± 0.9
Normal controls	29†	4.4 ± 0.3	5.2 ± 0.3

* No. of years hospitalized: median, 9; range, 2 to 27.
† No. of urine collections: chronic schizophrenia, 173; acute schizophrenia, 23; normal controls, 126.

In order to determine the effect of diet on the rate of excretion of 5-HIAA, three normal subjects were maintained for 3 days on each of the following diets with suitable control periods before and between the diets: (i) high carbohydrate, (ii) high fat, (iii) high protein, and (iv) 750 mg/day of L-tryptophan. No unusual effects were found, and all 5-HIAA values were well within the normal range.

In a longitudinal study carried on for 5 weeks, 20 urine samples were collected from each of two chronic schizophrenic patients and from one normal subject, a hospital attendant who ate approximately the same food as the patients. Patient No. 1 excreted an average of 11.0 mg of 5-HIAA per day with a range of 0.7 to 18.9 mg/day. Patient No. 2 excreted 8.6 mg/day with a range of 2.2 to 16.9 mg/day. No correlation between the patients' psychiatric behavior and urinary excretion of 5-HIAA could be demonstrated. The normal subject excreted an average of 5.9 mg/day with a range of 3.1 to 9.8 mg/day.

We also studied the effect of LSD on 5-HIAA excretion in four normal subjects, each of whom received 75 μg of LSD orally. Urine samples were collected immediately before the administration of LSD and 2 hours after. The typical symptoms of the LSD psychosis were evident in less than 2 hours. No significant change in 5-HIAA excretion was observed.

The evidence based on urinary 5-HIAA excretion in chronic and acute schizophrenic patients does not indicate a causal relationship between serotonin and schizophrenia. Preliminary results indicate also that blood serotonin values of chronic schizophrenic patients, measured by the fluorimetric method of Udenfriend and coworkers (*11*), do not differ significantly from those of normal subjects; the values of both groups ranged between 0.1 and 0.3 μg/ml of blood. However, serotonin metabolism, as measured by serotonin levels in blood and by 5-HIAA in urine, reflects serotonin primarily from the larger body stores. A hypothetical defect in mechanisms involving serotonin would most likely exist in the brain and might not be detectable by the methods employed.

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References and Notes

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