THE URINARY EXCRETION OF HISTAMINE IN SCHIZOPHRENIA

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It has frequently been observed that patients with schizophrenia are more tolerant of the effects of histamine than are normal people (Hill, 1940; Hoch, 1952; Lucy, 1954; Rouleau, Delâge, Bouchard, Coulombe, and Nadeau, 1954). For example, Lucy (1954) gave 28 mg. of histamine base to a schizophrenic patient—a dose four times as great as any previously recorded—and there were no side-effects other than a fall in blood pressure. This increased tolerance may be related to the general lack of responsiveness to biochemical stimuli shown by schizophrenics or it may indicate some abnormality of the metabolism of histamine. Adam (1950) concluded that information about the role of histamine in the pathogenesis of disease might be obtained by investigating the excretion of free histamine in the urine. The present work was undertaken to determine whether an abnormal metabolism of histamine in schizophrenia could be demonstrated by this means.

Methods and Procedure

Free histamine was extracted from urine by a chromatographic method in which histamine is adsorbed on a cation exchange column and subsequently eluted and dried (Roberts and Adam, 1950). The extracted histamine is concentrated by taking it up in a smaller volume than that of the original urine, and assayed biologically on a strip of guinea-pig's ileum suspended in a bath of atropinized Tyrode solution. In preliminary tests using this method, $63.4\% \pm 2.8$ of histamine added to urine was recovered, a rate similar to that of $67\% \pm 1.1$ reported by Roberts and Adam (1950). This recovery rate of approximately two-thirds is a characteristic of the method and a correction factor can be applied if necessary. All the values for histamine in this paper are uncorrected and are expressed in terms of the free base, unless otherwise stated.

A modified form of the histamine excretion test described by one of us (Mitchell, 1956a) was used in the investigation. The subject fasted for at least 10 hours before the test began, and throughout its duration, only water being allowed by mouth. At 8 a.m. the bladder was emptied and the urine discarded. At 10 a.m. urine was passed into a bottle containing a few millilitres of

2N HCl. During the next two hours, histamine acid phosphate was injected subcutaneously, the total dose of 20 μ g. per kg. of body weight being divided into four equal injections, which were given at intervals of half an hour (at 10, 10.30, 11, and 11.30 a.m.). At 12 noon, urine was again collected, thus giving two two-hour samples for the extraction of histamine.

Sixteen male patients with schizophrenia were tested during the investigation. Their ages ranged from 18 to 54 years and the duration of the illness was from two to 19 years. All had been under observation for at least two years and in every case several psychiatrists had concurred in the diagnosis. The group comprised patients with hebephrenic, catatonic, paranoid, and simple types of schizophrenia. All showed the typical schizophrenic thought disorder and at some time all had shown the more florid signs and symptoms, such as delusions, hallucinations, excitement, and stupor. At the time of the investigation, however, some were listless, apathetic and asocial.

The modified histamine excretion test outlined above was carried out on nine of the patients and on nine healthy men, aged from 31 to 46 years. It was noteworthy that the patients made no complaint and only local wealing was observed as a result of the histamine injections, whereas the healthy men experienced headache and flushing.

In a second series of experiments, the excretion test was carried out on five more of the patients with schizophrenia, using a total dose of histamine acid phosphate of 10 μ g. per kg. instead of 20 μ g. per kg. as used in the first series. Half an hour before the first injection (at 9.30 a.m.) the patient was given an oral dose of the histaminase-inhibiting drug, aminoguanidine bicarbonate, 10 mg. being given per kg. of body weight.

Finally, histamine excretion tests were made on two further patients but instead of four injections of histamine during the second two-hour period, a single injection of 2.5 mg. of histamine acid phosphate was given at 10 a.m. in each case, this dose representing 47 μ g. and 34 μ g. per kg. respectively.

In every instance, extraction of free histamine from the urine was completed on the day the clinical test was carried out. To eliminate any possible bias, one of us conducted the clinical tests and did not know the results of the assays until the investigation was completed; the other extracted and assayed the histamine without knowing the source of the urine sample.

TABLE I

EFFECT OF SUBCUTANEOUS INJECTION OF HISTAMINE ACID PHOSPHATE ON EXCRETION OF FREE HISTAMINE IN URINE OF SCHIZOPHRENICS AND OF HEALTHY MEN

Subjects	Total Dose of Histamine Acid Phosphate Injected during Period II (mg.)	Free Histamine in Urine (μ g.)		Extra Free Histamine Excreted in Period II as Percentage of Dose Injected
		Period I 8-10 a.m.	Period II 10 a.m.-12 noon	
<i>Schizophrenics</i>				
1	1.40	0.58	2.75	0.68
2	1.30	0.44	2.10	0.56
3	1.15	0.51	2.71	1.21
4	1.25	1.22	2.43	1.47
5	1.70	0.46	3.44	0.76
6	1.12	0.88	3.29	0.94
7	1.06	0.95	1.84	0.37
8	1.25	0.55	4.13	1.25
9	1.29	1.24	4.50	1.10
Mean	1.28	0.76	3.47	0.93
<i>Healthy men</i>				
1	1.30	1.16	3.52	0.79
2	1.66	0.81	4.20	0.89
3	1.44	1.35	7.14	1.75
4	1.40	0.72	2.87	0.67
5	1.08	0.43	2.16	0.70
6	1.10	1.26	4.56	1.31
7	1.30	0.44	3.30	0.96
8	1.06	0.52	2.50	0.82
9	1.41	0.72	6.50	1.79
Mean	1.31	0.82	4.08	1.08

Results

The results of the first series of experiments are recorded in Table I. It can be seen that there is no significant difference between the mean doses of histamine acid phosphate for the two groups, indicating that the mean body weight of the nine schizophrenic patients was virtually the same as that of the nine healthy men. This close correspondence was fortuitous, because no attempt was made to match the subjects by weight, and selection was made on no other basis than clinical suitability in the case of the patients and convenience in the case of the healthy volunteers. The mean amount of free histamine excreted by the patients during the first period of two hours was 0.76 μ g., the range being from 0.44 to 1.24 μ g. The amounts excreted by the healthy men ranged from 0.43 to 1.35 μ g., the mean value being 0.82 μ g. There is no significant difference between these two series and the ranges of values are similar to those found previously for

the basal excretion of free histamine by healthy men (Mitchell and Code, 1954; Mitchell, 1956a).

The amount of extra free histamine excreted during period II as a result of the injections was estimated by subtracting the value for period I from that for period II. The mean amount excreted by the schizophrenic patients was 2.71 μ g., while that excreted by the healthy men was 3.28 μ g. When

the values are multiplied by $\frac{100}{63.4}$ (to correct for loss

by the method) and converted to terms of histamine acid phosphate (assuming that this contains 36.16% of the base) they can be expressed as a percentage of the total dose of histamine acid phosphate injected. Calculated in this way, the mean percentage of the dose excreted by the patients was 0.93% and by the healthy men was 1.08%. The difference between these mean values is not statistically significant ($P = 0.4$) nor do they differ significantly from the mean value of 0.96% found in 12

TABLE II

EFFECT OF DOSES OF AMINOGUANIDINE BICARBONATE ON EXCRETION OF HISTAMINE INJECTED SUBCUTANEOUSLY INTO SCHIZOPHRENICS

Patient	Total Dose of Histamine Acid Phosphate Injected during Period II (mg.)	Dose of Aminoguanidine Given Orally at 9.30 (mg.)	Free Histamine in Urine (μ g.)		Extra Free Histamine Excreted in Period II as Percentage of Dose Injected
			Period I 8-10 a.m.	Period II 10 a.m.-12 noon	
10	0.57	570	0.48	4.74	3.26
11	0.53	530	0.75	4.15	2.80
12	0.52	520	0.22	2.20	1.64
13	0.92	920	0.56	5.82	2.49
14	0.53	530	1.00	4.90	3.21
Mean	0.61	614	0.60	4.36	2.68

histamine excretion tests on other healthy men, with doses of histamine acid phosphate ranging from 5 to 20 μ g. per kg. (Mitchell, 1956a).

When the histamine was injected as a large single dose the proportion excreted was essentially the same. The two patients given 2.5 mg. of histamine acid phosphate excreted 7.23 and 4.77 μ g. of extra free histamine during period II, representing respectively 1.26% and 0.83% of the dose injected.

The results of the experiments with aminoguanidine are shown in Table II. When aminoguanidine was given before the histamine injections, the mean percentage of the dose excreted as free histamine was 2.68, a mean value similar to that of 3.05% found in similar tests on healthy men (Mitchell, 1956b).

Discussion

The physiopathology of the schizophrenias has been intensively studied over many years in the search for an organic basis for these disorders. The high incidence during adolescence and at the menopause suggests that the endocrine system is involved, but, although the association of endocrine disease and schizophrenia has often been reported, no consistent relationship has been established. Therapeutic administration of every conceivable gland preparation has been tried without success and many biologically active substances, such as acetyl choline and histamine, have been used with conflicting results.

Metabolic studies have been similarly unproductive and a review by Hoskins (1946) of his own and other authors' work in this field revealed very little of aetiological significance. A notable exception is the demonstration by Gjessing (1935, 1947) that there is a disturbance of nitrogen metabolism in periodic catatonia. This condition, however, probably accounts for less than 2% of all cases of schizophrenia. The only constant finding has been that the schizophrenic patient is less responsive to stimuli such as heat, cold, thyroid extract, insulin, and adrenaline. In the case of histamine the lack of response has been described as "staggering" (Lucy, 1954), tolerance of doses in excess of 20 mg. of histamine base being commonplace. Lucy's work shows that this abnormal tolerance of histamine increases with the duration of the illness, and he concludes that on the available evidence it appears to be a non-specific reaction.

Our experiments indicate that the pattern of histamine metabolism in schizophrenia does not

differ from the normal. The basal excretion of free histamine in the urine of the schizophrenic men was similar to that of the healthy men, indicating that the usual amounts of histamine were being liberated from the tissues into the blood stream. The schizophrenic patients excreted injected histamine normally, and the fact that the proportion of the dose excreted increased by the expected amount when histaminase was inhibited by aminoguanidine suggests that there was no disturbance of histaminase activity.

It appears probable therefore that the increased tolerance of histamine shown in schizophrenia is simply a manifestation of a general lack of responsiveness rather than a specific metabolic defect.

Summary

Free histamine was measured in the urine of 16 men with schizophrenia, before and after the subcutaneous injection of histamine.

Values for the basal excretion of free histamine and the percentage of the injected dose which was excreted did not differ significantly from those recorded for healthy men.

When the histaminase-inhibiting drug, aminoguanidine, was given before injecting the histamine, the mean percentage of the dose excreted increased from 0.93 to 2.68, a change comparable with that occurring in healthy men.

No abnormality of histamine metabolism has therefore been found in schizophrenia, and it appears that the increased tolerance of histamine shown by schizophrenics is part of a general lack of tissue responsiveness.

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