URINARY TRYPTOPHAN METABOLITES IN RHEUMATOID ARTHRITIS AND SOME OTHER DISEASES

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Previous studies from this laboratory have shown that a majority of patients with rheumatoid arthritis excrete abnormally high amounts of 3-hydroxyanthranilic acid and kynurenine (Bett, 1962a, b). A more striking finding was the rise in kynurenine output after tryptophan loading in rheumatoid arthritis. Administration of large doses of pyridoxine over a short period caused a temporary fall in kynurenine output which increased again when the test was repeated after pyridoxine had been withdrawn for a week.

Urinary tryptophan metabolites have been studied in a variety of diseases including rheumatoid arthritis and it is known that abnormalities in the metabolism of this amino acid are not specific to this particular disease. Flinn, Price, Yess, and Brown (1964) refer to studies in which increased amounts of several metabolites were found in the urine of patients with bladder cancer, scleroderma, acrosclerosis, porphyria and lupus erythematosus, and in pregnant women. No abnormalities were found in patients with psoriasis, atopic dermatitis, hyperthyroidism, muscular dystrophy, Friedrich's ataxia, or diabetes mellitus. These authors also measured kynurenic acid, xanthurenic acid, indoxyl sulphate, anthranilic acid glucuronide, o-aminohippuric acid, N- α -acetyl kynurenine, kynurenine, 3-hydroxykynurenine, and pyridone in the urines of fifteen female and five male patients with rheumatoid arthritis. After tryptophan loading they found significantly raised levels of one or more of the metabolites measured in twelve of the fifteen female patients and in four of the five male patients. Kynurenine and 3-hydroxykynurenine were most frequently elevated. Pyridoxine restored metabolism to normal in eleven female patients studied, although it had been shown previously that excretion of 4-pyridoxic acid was normal in these patients. Spiera (1963) and Spiera and Plotz (1964) found that a significant number of

patients with rheumatoid arthritis excreted increased quantities of kynurenine, 3-hydroxyanthranilic acid, and xanthurenic acid as compared with patients suffering from other connective tissue diseases and with a group of patients with other diseases. Pinals (1964) has also measured a series of tryptophan metabolites in patients with rheumatoid arthritis, other connective tissue disease, and other diseases, and concluded that kynurenine and 3-hydroxykynurenine were excreted in increased amounts non-specifically in rheumatoid arthritis. Excretion did not correlate well with indices of clinical activity of disease.

In the present study kynurenine, 3-hydroxykynurenine, kynurenic acid, xanthurenic acid, anthranilic acid, and N-methylnicotinamide (pyridone) have been measured before and after 3 g. L-tryptophan given by mouth in patients suffering from rheumatoid arthritis, patients with other diseases affecting connective tissue, and patients with a variety of other diseases. For technical reasons 3-hydroxyanthranilic acid was not measured concurrently.

Materials and Methods

Members of the staff of the Northern General Hospital, Edinburgh, served as healthy controls. Patients suffering from rheumatoid arthritis and the majority of patients with other diseases of connective tissue were attending the same hospital. The remainder were referred from other hospitals in the region. While under observation the majority of patients with rheumatoid arthritis were receiving salicylates. It has been shown previously that this drug does not interfere with the metabolism of tryptophan or with measurement of tryptophan metabolites in urine (Bett, 1962b).

Urine was collected over 24-hour periods from all subjects immediately before and after the ingestion of 3 g. L-tryptophan. Toluene was used as a preservative. Aliquots stored for any length of time in the refrigerator for the determination of all metabolites except pyridone were acidified (normal hydrochloric acid). Urine for

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pyridone measurement was stored at 4° C. under toluene.

Kynurenine, 3-hydroxykynurenine, kynurenic acid, xanthurenic acid, and anthranilic acid for use in standard solutions were obtained commercially. N-methylnicotinamide (pyridone) was synthesized by the method of Holman and Wiegand (1948).

Kynurenine was measured by the method of Tompsett (1959) in urine which had been hydrolysed in N-hydrochloric acid for 1 hour. Kynurenic acid, xanthurenic acid, anthranilic acid, and 3-hydroxykynurenine were also measured on acid-hydrolysed urine by the chromatographic methods described by Brown and Price (1956), Brown (1957), and Satoh and Price (1958). These four metabolites were eluted from the same set of Dowex columns. As acid-hydrolysed urine was used in the following experiments, conjugated derivatives of these metabolites are therefore included in the results. Pyridone was measured in unhydrolysed urine by the method of Price (1954). Columns were washed with 200 ml. distilled water instead of 100 ml. as used in the above method. This was found to be necessary to obtain satisfactory recoveries. Recovery experiments for all metabolites were made with each specimen of urine.

Results

The mean kynurenine output in 35 healthy subjects was found to be 1.5 ± 1.3 mg./24 hrs. In 59 patients suffering from rheumatoid arthritis the mean output was 4.7 ± 4.2 mg./24 hrs. The distribution of results in the patients with rheumatoid arthritis is bimodal (Fig. 1). Only 17 per cent. of control subjects excreted more than 2 mg./24 hrs, but 69.6 per cent. of patients excreted more than this amount. Kynurenine output was again measured after an oral dose of 3 g. L-tryptophan. Here, and in all subsequent tables and results, kynurenine output (or output of other metabolites) after L-tryptophan will refer to the difference in output in the 24 hrs before and after a loading dose of 3 g. L-tryptophan. The mean output in the 35 healthy subjects was 25.1 ± 23.3 mg./24 hrs. In the 59 patients with rheumatoid arthritis this output was 99.1 ± 58.4 mg./24 hrs. The distribution of these results again appeared to be bimodal (Fig. 1). Of the patients with rheumatoid arthritis, 71.2 per cent. excreted more than 60 mg./24 hrs, whereas only 5.7 per cent. of healthy subjects excreted more than this amount.

The mean output of 3-hydroxykynurenine in 35 healthy subjects was 7.4 ± 5.8 mg./24 hrs compared with 14.8 ± 12.9 mg./24 hrs in 51 patients with rheumatoid arthritis. 54.9 per cent. of these patients excreted more than 10 mg./24 hrs, but only 20 per cent. of the healthy subjects excreted more than this amount. After L-tryptophan the mean output for 35 healthy subjects was 19.3 ± 19.5 mg. and for 51 patients with rheumatoid arthritis it was

Fig. 1.—Output of urinary kynurenine before and after 3 g. L-tryptophan in patients with rheumatoid arthritis and in healthy control subjects.

122.4 ± 75.9 mg. More than 60 mg./24 hrs was excreted by 84.2 per cent. of the patients with rheumatoid arthritis, but by only 5.7 per cent. of the healthy control subjects. The distribution of these results is illustrated in Fig. 2.

Fig. 2.—Output of 3-hydroxy-kynurenine before and after 3 g. L-tryptophan in patients with rheumatoid arthritis and in healthy control subjects.

The basal output of kynurenic acid and xanthurenic acid did not differ between the two groups. After L-tryptophan the mean output of kynurenic acid was 13.7 mg./24 hrs in the healthy subjects and 47.0 mg./24 hrs in the patients with rheumatoid arthritis. Of patients with rheumatoid arthritis 84.9 per cent. excreted more than 20 mg./24 hrs compared with 20 per cent. of the healthy subjects. The mean output of xanthurenic acid after tryptophan was 12.0 mg./24 hrs in 35 control subjects and 31.4 mg./24 hrs in 49 patients with rheumatoid arthritis. Only 11.4 per cent. of the control subjects excreted more than 20 mg./24 hrs of this metabolite, whereas 61.2 per cent. of the patients with rheumatoid arthritis excreted more than this amount. The distribution of results for kynurenic acid and xanthurenic acid before and after tryptophan is illustrated in Figs 3 and 4.

Fig. 3.—Output of kynurenic acid before and after 3 g. L-tryptophan in patients with rheumatoid arthritis and in healthy control subjects.

Anthranilic acid output was measured in 22 healthy subjects and 24 patients with rheumatoid arthritis. There was no apparent difference between the two groups either before or after loading with L-tryptophan (Fig. 5).

N-methyl-2 pyridone-5 carboxamide was measured in twenty healthy subjects and 22 patients with rheumatoid arthritis. There was no difference in excretion between the two groups before or after loading, indicating that the patients with rheumatoid

Fig. 4.—Output of xanthurenic acid before and after 3 g. L-tryptophan in patients with rheumatoid arthritis and in healthy control subjects.

Fig. 5.—Output of anthranilic acid before and after 3 g. L-tryptophan in patients with rheumatoid arthritis and in healthy control subjects.

arthritis converted tryptophan to niacin normally (Fig. 6, opposite).

The bulk of ingested tryptophan was excreted in this pathway as kynurenine and 3-hydroxykynurenine. A further analysis of results was made on the basis of the percentage of the tryptophan load excreted as the sum of these two metabolites. Of male patients with rheumatoid arthritis 21 per cent. (4/19) excreted less than 2 per cent. of the load in this

Fig. 6.—Output of pyridone before and after 3 g. L-tryptophan in patients with rheumatoid arthritis and in healthy control subjects.

form, whereas 92 per cent. (12/13) of healthy males excreted less than this percentage. The 23 healthy females all excreted less than 4 per cent. of the load as kynurenine plus 3-hydroxykynurenine, but only 12.5 per cent. (4/32) of the female patients with rheumatoid arthritis excreted less than this percentage. There tends to be a higher excretion in females than in males, both in healthy subjects and in patients with rheumatoid arthritis (Fig. 7).

Fig. 7.—Percentage of 3 g. L-tryptophan excreted as kynurenine plus 3-hydroxy-kynurenine in patients with rheumatoid arthritis and in healthy controls.

It was previously shown (Bett, 1962b) that there was no correlation between kynurenine output and activity of disease, as measured by erythrocyte sedimentation rate and haemoglobin level, nor was there any correlation with age, duration of disease, grade of functional capacity, sensitized sheep cell titre, presence of nodules, or x-ray changes typical of rheumatoid arthritis. On the basis of output of

kynurenine plus 3-hydroxykynurenine, there was no apparent difference in these indices or in the clinical presentation between patients with normal and abnormal patterns.

Some patients, however, have been observed who have improved clinically. When tryptophan-load tests were carried out before and after improvement in clinical status, the kynurenine output tended to fall following improvement in haematological indices. The mean kynurenine output in fourteen patients before treatment was 118.6 mg./24 hrs, the corresponding mean haemoglobin level and erythrocyte sedimentation rate being 76 per cent. and 66 mm. in the 1st hour respectively. With clinical improvement the mean kynurenine output fell to 65.7 mg./24 hrs and the mean haemoglobin level and erythrocyte sedimentation rate became 86 per cent. and 17 mm. in the 1st hour respectively.

Pyridoxine

It was shown previously (Bett, 1962b) that administration of large amounts of pyridoxine (100 mg. daily) intramuscularly, and in some cases orally, was effective in decreasing abnormally high outputs of kynurenine after tryptophan load in these patients—usually to within the normal range. Kynurenic acid, xanthurenic acid, and 3-hydroxykynurenine as well as kynurenine were measured in two patients after smaller amounts (10 mg. daily) over a shorter period with similar results. The output of all four metabolites, which were originally abnormal, fell to within normal limits after pyridoxine had been given orally for 6 days in a daily dose of 10 mg.

As a measure of dietary intake of pyridoxine, 4-pyridoxic acid was measured in a few subjects, using the method of Reddy, Reynolds, and Price (1958). The output before and after 3 g. L-tryptophan was measured in four patients with rheumatoid arthritis and abnormal tryptophan metabolism, and in one healthy subject and three patients with other diseases who had normal tryptophan metabolism. There was no difference in 4-pyridoxic acid output between the two groups, suggesting that dietary intake was adequate in patients with abnormal tryptophan metabolism.

It was observed previously (Bett, 1962b) that, when pyridoxine was given for a short time and then withdrawn, kynurenine output returned to previous high levels. Two patients were given 100 mg. pyridoxine by mouth daily for 10 to 30 weeks, and kynurenine output, which was high in both instances, fell to normal levels, and has remained normal for 18 months to 2 years after pyridoxine withdrawal. These patients, however, did not have clinically active disease during this time. The results of a

more detailed assessment of two patients given 100 mg. pyridoxine by mouth for 11 months are shown in Table I. Fall in kynurenine output was not necessarily accompanied by improvement in haematological indices.

Other Diseases of Connective Tissue

Kynurenine output was measured after tryptophan loading in 27 patients with diseases of connective tissue other than rheumatoid arthritis (Table II). Output of kynurenine exceeded 60 mg./24 hrs in sixteen patients. The normal excretion observed in three patients suffering from ankylosing spondylitis may be misleading as they were all receiving phenylbutazone, a drug whose metabolites may interfere with the measurement of urinary kynurenine.

Diseases Other than Those affecting Connective Tissue

38 patients were studied (Table II). Sixteen patients had an abnormally high excretion of kynurenine after tryptophan loading. The numbers in individual diagnostic categories are small, but it is seen that abnormal outputs are common in patients with pyridoxine-responsive anaemia and in the malabsorption syndrome, where pyridoxine deficiency may reasonably be suspected. Three cases of bronchial carcinoma had normal tryptophan metabolism, but a further case with associated pulmonary osteo-arthritis excreted increased amounts of kynurenine and 3-hydroxykynurenine. This patient excreted large amounts of these metabolites after tryptophan loading. After radiotherapy there was relief of skeletal symptoms and radiological evidence of decrease in tumour size; excretion then became normal, but 3 months later symptoms and signs recurred and excretion of tryptophan metabolites was again increased (Table III, opposite).

If patients with pyridoxine-responsive anaemia and with malabsorption syndrome are excluded, examination of Table II suggests that abnormal excretion of kynurenine after loading with tryptophan is most commonly observed in diseases characterized by

TABLE II
KYNURENINE OUTPUT (AFTER TRYPTOPHAN LOADING) IN RHEUMATOID ARTHRITIS, IN OTHER DISEASES AND IN HEALTHY SUBJECTS

Diagnosis	Total Cases	Abnormal Kynurenine Output	
		No.	Percentage
Rheumatoid Arthritis	59	44	74.7
Other Diseases of Connective Tissue			
Systemic lupus erythematosus ..	3	3	
Dermatomyositis	3	3	
Scleroderma	1	0	
Polymyalgia rheumatica	2	2	
Myositis	3	2	
Rheumatic fever	1	0	
Behçet's syndrome	1	1	
Psoriatic arthropathy	5	4	
Erythema nodosum	1	0	
Degenerative disk disease	3	1 ⁽¹⁾	
Ankylosing spondylitis	3 ⁽²⁾	0	
Ehlers-Danlos syndrome	1	0	
Total	27	16	59.3
Other Diseases			
Haemachromatosis	3	0	
Pernicious anaemia	3	1	
Miscellaneous anaemias	4	0	
Polycythaemia	1	0	
Chronic lymphatic leukaemia	1	0	
Diabetes	2	0	
Subarachnoid haemorrhage	1	0	
Myocardial infarct	1	0	
Carcinoid syndrome	1	0	
Osteomyelitis	1	0	
Pyridoxine-responsive anaemia	3	3	
Malabsorption	5	4	
Bronchial carcinoma	4	1 ⁽³⁾	
Chronic bronchitis	3	3	
Bronchiectasis	2	2	
Pulmonary fibrosis	1	0	
Myeloma	1	1	
Cholelithiasis presenting with myalgia	1	1	
Total	38	16	42.1
Healthy Subjects	35	2	5.7

⁽¹⁾ Positive sensitized sheep cell test, but no clinical evidence of rheumatoid arthritis.

⁽²⁾ On phenylbutazone.

⁽³⁾ Accompanied by osteo-arthritis.

inflammation and/or cellular proliferation. Of 97 patients in the study with such diseases, 70 per cent. excreted more than 60 mg./24 hrs kynurenine compared with 10 per cent. of nineteen patients with other diseases. The kynurenine output was abnormal in all but one of a further group of eight cases.

TABLE I
RELATIONSHIP BETWEEN KYNURENINE OUTPUT, ERYTHROCYTE SEDIMENTATION RATE (ESR), AND HAEMOGLOBIN (Hb) LEVELS IN TWO PATIENTS WITH RHEUMATOID ARTHRITIS GIVEN 100 mg. PYRIDOXINE DAILY

Months on Pyridoxine (100 mg./day orally)	Patient 1			Patient 2		
	Kynurenine Output	ESR (mm./hr)	Hb Percentage of 14.6 g.	Kynurenine Output	ESR (mm./hr)	Hb Percentage of 14.6 g.
0	114.7	88	65	168.9	51	73
3	22.5	59	83	22.4	28	84
6	14.7	44	89	40.9	49	76
9	2.0	46	101	32.6	36	68
11	18.2	58	95	22.1	45	68

TABLE III
TRYPTOPHAN METABOLISM IN A CASE OF HYPERTROPHIC PULMONARY OSTEO-ARTHROPATHY (F.60)

Clinical Condition		Output (mg./24 hrs)					
		K	30HK	KA	XA	AA	Pyridone
Skeletal symptoms with radiological evidence of bronchogenic carcinoma. (ESR 40)	Basal After 3 g. L-Tryptophan	2.8	70.3	3.4	8.9	9.3	6.7
		151.5	330.0	57.6	91.8	7.0	27.2
Radiotherapy with relief of skeletal symptoms and evidence of decrease in size of tumour. (ESR 13)	Basal After 3 g. L-Tryptophan	1.5	2.6	2.5	4.5	0.7	2.0
		30.3	36.6	8.5	11.8	1.7	10.0
3 months later—recurrence of skeletal symptoms and evidence of increase in size of pulmonary opacity. (ESR 26)	Basal After 3 g. L-Tryptophan	6.7	39.3	10.7	13.1	9.8	8.1
		117.4	68.8	42.7	43.4	3.2	53.7

K = Kynurenine. 30HK = 3-hydroxykynurenine. KA = Kynurenic Acid. XA = Xanthurenic Acid. AA = Anthranilic Acid.

in which there was evidence of pyridoxine deficiency or malabsorption.

Discussion

In recent years there have been several reports of abnormalities of tryptophan metabolism in patients with rheumatoid arthritis without any satisfactory explanation for these abnormalities. Flinn and others (1964) suggested that these patients had a functional deficiency of pyridoxine. Spiera (1963) and Spiera and Plotz (1964) offered as an explanation an increase in tryptophan pyrrolase activity. Tryptophan, for some unknown reason, was being deviated into the kynurenine pathway. Cortisone is known to increase tryptophan pyrrolase activity. In the present study, however, kynurenine output tended to fall in patients receiving corticosteroids. Pinals (1964) concluded from his studies that kynurenine and 3-hydroxykynurenine were excreted in increased amounts non-specifically in rheumatoid arthritis. Excretion did not correlate well with indices of clinical activity of disease. His explanation was inhibition of pyridoxal-dependent hepatic enzyme by some unknown mechanism.

McKusick, Sherwin, Jones, and Hsu (1964) measured urinary pyridoxine and 4-pyridoxic acid in seven patients with rheumatoid arthritis and seven paired control subjects. The patients with rheumatoid arthritis excreted significantly less pyridoxine than the control subjects on an identical constant diet. There was some suggestion that pyridoxine output increased when clinical improvement occurred. These authors suggested that low urinary pyridoxine does not necessarily mean low availability in the body, and that it could be used up at an unusually rapid rate in these patients by some other metabolic or immunological process.

The results in the present series tend to support this supposition. Although tryptophan metabolism was abnormal there was no apparent dietary deficiency of pyridoxine. Hsu, Davis, and Chow

(1958) found that serum glutamic oxalacetic transaminase (SGOT) levels were greatly reduced in rats maintained on a diet deficient in vitamin B₆. Subsequently SGOT levels have been used to indicate the availability of pyridoxine. A decrease in the activity of this enzyme system was interpreted as resulting from a decrease in the co-enzyme (Babcock, 1959). Baysal, Johnson, Yess, and Linkswiler (1964) found that serum transaminase decreased to one half the original value in individuals who had been on a vitamin B₆-depleted diet for 30 days. Serum transaminase levels measured in our patients with rheumatoid arthritis (Chalmers, unpublished) were not abnormally low. Wiss and Weber (1964), however, stated that increased kynurenine and 3-hydroxykynurenine were the first signs of inadequate supply of pyridoxine in animals and humans. This suggests that any pyridoxine "deficiency" in patients with rheumatoid arthritis is a relatively mild one. Patients whose tryptophan metabolism became normal on pyridoxine did not necessarily improve clinically. On the other hand, in those who did improve, kynurenine excretion tended to fall.

Pyridoxine is necessary for many biological functions and acts as a co-enzyme in many reactions. Antibody response is impaired in pyridoxine deficiency, as is cellular proliferation (Axelrod, Hopper, and Long, 1961). Anti-tumour effects have been ascribed to pyridoxine deficiency (Stoerk, 1947), and more recently Gailani and Holland (1964) have tried to evaluate the anti-tumour effects of pyridoxine deficiency in man. Using a pyridoxine-deficient diet alone, exploratory trials were negative in five patients. However, the patient with bronchial carcinoma and pulmonary osteo-arthropathy, described above, obtained relief of skeletal symptoms after radiotherapy and there was a decrease in tumour size. It could be postulated here that pyridoxine was being used up for cellular proliferation, thus creating a relative deficiency for amino acid breakdown.

When there was a reduction in the number of tumour cells after irradiation, pyridoxine again became available for amino acid breakdown.

The presence of the rheumatoid factor in the serum of patients with rheumatoid arthritis suggests that there may be some disordered immune response in this disease associated with a higher than normal uptake of pyridoxine. It may, however, be postulated that the gross cellular proliferation occurring in the joints of patients suffering from rheumatoid arthritis is sufficient to account for the apparent "pyridoxine deficiency" described. The fact that tryptophan metabolism tended towards normal in those cases in which clinical improvement occurred may support this theory.

Summary

A series of tryptophan metabolites has been measured in the urine of a group of healthy control subjects and in a group of patients with rheumatoid arthritis before and after oral tryptophan loading. The majority of these patients excreted greater than normal amounts of several metabolites, notably kynurenine and 3-hydroxykynurenine. Administration of pyridoxine resulted in decreased excretion of these metabolites after loading. There was, however, no indication that these patients were receiving a diet deficient in pyridoxine. A fall in abnormally high excretion was also noted when there was decreased disease activity for any reason.

Excretion of these metabolites was also measured in a group of patients suffering from connective tissue disease other than rheumatoid arthritis and in a further group suffering from other diseases.

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Les métabolites urinaires du tryptophane dans l'arthrite rhumatoïdale et dans quelques autres maladies

RÉSUMÉ

On a mesuré le taux dans l'urine d'une série de métabolites du tryptophane dans un groupe de témoins et dans un groupe de malades atteints d'arthrite rhumatoïdale avant et après épreuves de surcharge per os par le tryptophane; la majorité de ces malades a excrété des quantités anormalement grandes de plusieurs métabolites, notamment de kynurénine et de 3-hydroxykynurénine. L'administration de pyridoxine provoqua une diminution du taux d'excrétion de ces métabolites après surcharge. Rien cependant n'indiqua que le régime de ces malades était déficient en pyridoxine. On nota aussi une régression de l'exagération de l'excrétion de ces métabolites lorsque pour une raison quelconque l'évolutivité de la maladie diminuait.

On a mesuré aussi l'excrétion de ces métabolites dans un groupe de malades souffrant d'une collagénose autre que l'arthrite rhumatoïdale et aussi dans un groupe de sujets présentant d'autres maladies. Les résultats sont rapportés et on discute leur portée.

Los metabolitos urinarios del triptofan en la artritis reumatoide y algunas otras enfermedades

SUMARIO

Se midieron en la orina ciertos metabolitos del triptofan en un grupo de testigos y en otro de enfermos con artritis reumatoide antes y después de tests de sobrecarga per os con triptofan; la mayoría de estos enfermos excretaron cantidades mayores que la normal de varios metabolitos, particularmente quinurenina y 3-hidroxi-quinurenina. La administración de piridoxina resultó en una disminución de la excreción de estos metabolitos después de la sobrecarga. Ahora bien, no hubo indicación de que estos enfermos recibieran una dieta deficiente en piridoxina. Se nota también una caída de la excreción exagerada de estos metabolitos al disminuir la actividad morbosa por cualquier causa.

También fué medida la excreción de estos metabolitos en un grupo de enfermos que padecían collagenosis que no era artritis reumatoide y en un grupo de sujetos con otras enfermedades. Los resultados son recojidos y su importancia discutida.