HYPERTAURINURIA IN RHEUMATOID ARTHRITIS

BY

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Patients with rheumatoid arthritis show several metabolic abnormalities, including abnormal tryptophan metabolism (Bett, 1962a, b; Flinn, Price, Yess, and Brown, 1964). This was postulated as due to a functional deficiency in vitamin B₆ (Flinn and others, 1964), and McKusick, Sherwin, Jones, and Hsu (1964) did in fact demonstrate low urinary B₆ in patients with rheumatoid arthritis. An alternative hypothesis, that the abnormality of tryptophan metabolism was the result of increased tryptophan pyrrolase activity due to the induction of this enzyme by increased fibrinogen breakdown, has also been proposed (editorial comment, *Arthritis and Rheumatism*, 1966).

The formation of taurine from cysteine in the body is another metabolic pathway which may depend on vitamin B₆ (Wiss and Weber, 1964) deficiency resulting in low urinary output of taurine. The main product from the metabolism of cysteine is sulphate and the relevant pathways, as established in the rat, are shown in Fig. 1. The decarboxylation stages involve pyridoxal phosphate as co-enzyme and are said to be particularly sensitive to B₆ deficiency (Wiss and Weber, 1964; Sörbo, 1965; and Berlow, 1967).

It seemed of interest to examine the urinary taurine and sulphate levels in patients with rheumatoid arthritis in view of the possible deficiency of vitamin B₆ in such patients.

Material and Methods

Clinical

Patients were selected who had definite rheumatoid arthritis as defined by the criteria of the American Rheumatism Association (Ropes, Bennett, Cobb, Jacox and Jessar, 1959). Two groups were studied: one from whom salicylates were withheld during the time of urine collection and for the previous 3 or 4 days, and a second who received aspirin in doses of 4 to 6 g. daily throughout the experiment.

Fig. 1.—Relevant pathways of cysteine metabolism (Berlow, 1967).

The control group consisted of members and relatives of the staff of the Rheumatic Diseases Unit.

Biochemical

24-hour specimens of urine were collected under toluene. Measurements were made immediately in most cases; where this was not possible the urines were stored in a refrigerator.

Total and inorganic sulphate were determined by the method of Bray, Humphris, Thorpe, White, and Wood (1952); the urine was diluted 1:5 in water before measurements were made.

Taurine was estimated by the method of Sörbo (1961) and creatinine by the method of Bonsnes and Taussky (1945).

Statistical

Tests of significance were carried out (for $P=0.05$) using the modified Students' "t" test for small samples. The formula is

$$t = \frac{x_1 - x_2}{S \sqrt{\frac{1}{n_1} + \frac{1}{n_2}}}$$

where x_1 and x_2 are the mean values of the estimations, n_1 and n_2 are the number of estimations in each group, and S is an estimate of the standard deviation based on both samples jointly.

Results

From a preliminary experiment it had been anticipated that aspirin might influence the results. Salicylate and its metabolites were shown not to interfere with the measurement of sulphate or taurine and to cause only an insignificant increase in the measurement of creatinine. It was clear, therefore, that any differences observed between groups would be metabolic in origin.

Apart from disease and the taking of aspirin, another difference between the controls and patients was in the matter of diet. The patients were on a hospital diet whereas the control subjects' diet was unrestricted. To obviate any effects due to this, the taurine/total sulphate ratio was calculated. This ratio indicates the proportion of cysteine being directed to the two main products of cysteine metabolism—sulphate and taurine—and hence should eliminate any differences in results due to variable cysteine intake.

The results obtained are given in the Table, which shows that males excreted higher amounts of total and inorganic sulphate than females (similar results are quoted by Cockburn, 1961). Males also excreted higher amounts of taurine than females. This difference was probably dietary since in control subjects the mean taurine/total sulphate ratio (0.07) was the same for males and females. This difference did, however, make it necessary to compare the

sexes separately when assessing the meaning of any change in taurine or sulphate output.

Patients with rheumatoid arthritis who were not receiving aspirin excreted significantly more taurine than controls; the taurine/total sulphate ratio was also markedly increased. Creatinine output was significantly lower. The total and inorganic sulphate levels were not significantly different. There is therefore no obvious difference in the conjugated sulphate output. Any differences in carbohydrate sulphate turnover, which might be indicated by this figure, are probably masked by the greater amount of conjugated sulphate formed in detoxication processes.

The hypertaurinuria found in patients with rheumatoid arthritis is obviously reduced by aspirin. This can be seen from the Table, where the mean taurine output and also the mean taurine/total sulphate ratio was lower in patients receiving aspirin. Statistically the ratio was significantly lower only for females.

The effect of aspirin on taurine excretion was studied in six individual patients. These results are illustrated in Fig. 2, which shows that administration of aspirin was followed by a decrease in excretion of taurine.

The taurine/total sulphate ratios were also lowered. The results from Patient 4, who also had amyloid disease, have not been used in compiling the Table.

Discussion

The increased urinary output of taurine in patients with rheumatoid arthritis does not support the suggestion that there is a deficiency of vitamin B₆ in this disease, although increased taurine synthesis might make less B₆ available for other metabolic pathways, e.g. tryptophan degradation.

Several possible explanations for hypertaurinuria may be given. Hurley and Williams (1955) postulated that in muscular dystrophy a block in the formation of creatinine (at the stage of creatine

COMPARISON OF SULPHATE AND TAURINE EXCRETION

Group		Sex	Total Sulphate* (g.SO ₄ ⁼ /24 hrs)	Inorganic Sulphate* (g.SO ₄ ⁼ /24 hrs)
Control		Male	2.23 (10) ± 0.61	1.76 (10) ± 0.54
		Female	1.43 (8) ± 0.33	1.15 (8) ± 0.23
Rheumatoid Arthritis	not receiving aspirin	Male	1.86 (7) ± 0.57	1.32 (7) ± 0.65
		Female	1.26 (10) ± 0.38	0.91 (10) ± 0.37
	receiving aspirin	Male	1.96 (10) ± 0.38	1.39 (10) ± 0.51
		Female	1.75 (7) ± 0.53	1.21 (7) ± 0.60

*Mean value (number in group) ± standard deviation.

Fig. 2.—Taurine output in six patients, showing the effect of aspirin. The duration of aspirin treatment and also sex and age are indicated for each diagram. Patient No. 4 also had amyloid disease and received ACTH at the same time as aspirin.

phosphate synthesis) led, with inadequate methionine metabolism, to increased taurine formation. Such a mechanism does not, however, accord with the present results, in which the tendency was for a high output of taurine to be associated with a high output of creatinine. Also, additional formation of cysteine from methionine would not lead to an increased taurine/sulphate ratio.

Other possibilities exist, including decreased conversion of taurine to taurocholic acid, but it would seem that the most likely explanation for the hypertaurinuria in rheumatoid arthritis is cellular damage. Thus, hypertaurinuria is found in such conditions as advanced carcinoma, liver disease, muscular dystrophy, paroxysmal myoglobinuria, and as a result of tissue damage due to irradiation (Sörbo, 1965). The high renal clearance of taurine

has been given as the reason for its being the predominant amino acid excreted in tissue destruction (Soupart, 1962). Overproduction of taurine through a primary metabolic abnormality cannot be ruled out.

The mode of action of aspirin in reducing the output of taurine is still unexplained. Aspirin may act as an inhibitor in the vitamin B₆ dependent reactions or may interfere in some other way with the pathway of cysteine metabolism. Alternatively, the effect of aspirin may be associated with the anti-inflammatory action of the drug. As yet there is insufficient evidence to establish any of these hypotheses and further investigation is obviously required.

Summary

(1) 24-hour taurine, total and inorganic sulphate, and creatinine output were measured in control

CONTROL SUBJECTS AND PATIENTS WITH RHEUMATOID ARTHRITIS

Conjugated Sulphate (Total—Inorganic) (g.SO ₄ /24 hrs)	Taurine* (g./24 hrs)	Taurine/Total Sulphate* Ratio	Creatinine* (g./24 hrs)
0.47 0.28	0.154 (10) ± 0.07† 0.108 (8) ± 0.06‡	0.07 (10) ± 0.02† 0.07 (8) ± 0.03‡	1.80 (18) ± 0.37† 1.18 (18) ± 0.19‡
0.54 0.35	0.262 (7) ± 0.10† 0.221 (10) ± 0.07‡§	0.14 (7) ± 0.05† 0.18 (10) ± 0.05‡§	1.53 (11) ± 0.29† 0.78 (10) ± 0.20‡
0.57 0.54	0.187 (10) ± 0.09 0.102 (7) ± 0.05§	0.10 (10) ± 0.03 0.06 (7) ± 0.02§	1.25 (16) ± 0.20 0.87 (7) ± 0.16

Significant differences were found between groups in vertical columns marked †, ‡, and §.

subjects and in two groups of patients with rheumatoid arthritis—those receiving no drugs and those taking aspirin.

(2) There was a difference between the sexes in excretion of these metabolites.

(3) The output of taurine and the taurine/total sulphate ratios were significantly greater in patients with rheumatoid arthritis than in the control group.

(4) Patients taking aspirin had a lower output of taurine and lower taurine/total sulphate ratios than patients taking no drugs.

(5) It is suggested that the hypertaurinuria results

from cell destruction, although an overproduction of taurine *per se* cannot be excluded.

I should like to thank Dr. J. J. R. Duthie and Dr. W. R. M. Alexander for their helpful advice and criticism, and Miss D. Leithhead for expert technical assistance.

During the period of this study, the Rheumatic Disease Unit, Northern General Hospital, Edinburgh, was in receipt of grants from the Medical Research Council, the Arthritis and Rheumatism Council, the Nuffield Foundation, and Boots Pure Drug Company Limited, and the author was supported by the McRobert Fellowship awarded by the Arthritis and Rheumatism Council.

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L'hypertaurinurie dans la polyarthrite rhumatoïde

(1) On détermina le taux urinaire de 24 heures de la taurine, du sulfate total et inorganique et de la créatinine chez des témoins et dans deux groupes de malades atteints de polyarthrite rhumatoïde; un de ces groupes ne recevait aucun médicament et l'autre prenait de l'aspirine.

(2) Il y avait une différence entre les sexes en ce qui concerne l'excrétion de ces métabolites.

(3) L'élimination de la taurine et le rapport taurine/sulfate total furent significativement plus élevés chez les malades atteints de polyarthrite rhumatoïde que chez les témoins.

(4) L'excrétion de la taurine et le rapport taurine/sulfate total furent plus bas chez les malades prenant de l'aspirine que chez ceux sans aucun traitement médicamenteux.

(5) On suggère que l'hypertaurinurie provient de la destruction cellulaire, bien qu'une surproduction de la taurine *per se* soit une possibilité.

Hipertaurinuria en la poliartritis reumatoide

(1) Se determinó la excreción urinaria de 24 horas de la taurina, del sulfato total e inorgánico y de la creatinina en testigos y en dos grupos de enfermos con poliartritis reumatoide; uno de estos grupos fué tratado con aspirina y el otro no recibía ninguna medicación.

(2) No se encontró diferencia alguna entre los sexos respecto a la excreción de estos metabolitos.

(3) La excreción de la taurina y el cociente taurina/sulfato total fueron significativamente mayores en enfermos con poliartritis reumatoide que en los testigos.

(4) La excreción de la taurina y el cociente taurina/sulfato total fueron menores en los enfermos tratados con aspirina que en los sin medicación.

(5) Se sugiere que la hipertaurinuria resulta de la destrucción celular, aunque una sobreproducción de la taurina por si mismo no se puede excluir.