Case report

Isolated defect in postsecretory reabsorption of uric acid

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SUMMARY A 26-year-old woman was found to have an abnormally sensitive excretory response to a rise in plasma urate with a markedly increased ratio of uric acid to creatinine clearance (exceeding 35%). Uric acid was studied before and after administration of pyrazinamide and benzbromarone. In the presence of pyrazinamide urinary uric acid decreased markedly just as in normal subjects. The uricosuric response to benzbromarone was reduced. No other renal tubular or metabolic abnormalities were found. It appears that the abnormality is related to an isolated defect in post-secretory reabsorption of urate.

In the previous paper we give evidence for 4 components in the renal handling of uric acid in man (Levinson and Sorensen, 1979). According to that formulation 2 reabsorptive sites for urate reabsorption exist within the nephron, 1 proximal to and 1 distal to the secretory locus. Recent reports of defects in urate reabsorption in man lend credence to the proposed scheme for renal handling of urate.

One defect appears to involve diminished reabsorption of the filtered urate, in that urate excretion was not significantly reduced when secretion of urate was blocked by administration of pyrazinamide (Greene *et al.*, 1972; Sperling *et al.*, 1974; Benjamin *et al.*, 1977). A second defect exists in patients with urate clearances higher than the glomerular filtration rate (Praetorius and Kirk, 1950; Khachadurian and Arslanian, 1973; Simkin *et al.*, 1974). This defect appears to involve markedly impaired reabsorption of both filtered and secreted urate throughout the nephron. In the present communication we report a third defect in reabsorption of urate, distinctly located at the postsecretory site, in an otherwise healthy woman. A similar defect has been found in some patients with Wilson's disease (Wilson and Goldstein, 1973) and Hodgkin's disease (Bennett *et al.*, 1972) who have increased renal clearance of

uric acid. When such patients were given pyrazinamide, the urine became almost free of urate, indicating that their inappropriate handling of urate in the kidney did not result from a defect in tubular reabsorption of filtered urate.

Case report and methods

The patient was a 26-year-old woman who had been well throughout her life. Physical examination and routine haematological and blood chemistry values were within the normal range. She was 155 cm tall and weighed 55 kg. The mean of 22 creatinine clearances was 94.2 ml/min (112 ml/min corrected to a surface area of 1.73 m²). A number of special laboratory tests were performed and reported as normal. These included serum Cu 19.5 µmol/l; caeruloplasmin 2.57 µmol/l; urinary Cu 1.1 µmol/24 h; urinary calcium on average diet 2.68 mmol/24 h; urinary phosphorus 14.6 mmol/24 h; normal display of the glucose tolerance test curve. Chromatography of the urine yielded a normal pattern of nonhydrolysed amino acids in expected amounts for the solute concentration. A 24-hour specimen of urine contained 4.73 mmol of amino acids.

The patient was studied first at her endogenous plasma urate level while on a regular diet. Then yeast RNA, first 8 g/day and later 16 g/day, given in 4 daily doses, was added in order to increase plasma urate. Studies with pyrazinamide and benz-

Accepted for publication 4 May 1979.

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bromarone were carried out as described previously (Levinson and Sorensen, 1979). In clearance studies a urine flow of 4 to 6 ml per minute was induced by oral hydration. Informed written consent was obtained for all studies.

Results

Fig. 1 shows the response of uric acid excretion as a function of plasma urate concentration before and after RNA loading and for comparison the response of 10 normal subjects who had received 8 g RNA daily for 5 days. All data are expressed per unit of glomerular filtration to correct for differences in nephron population. Also shown is the typically sluggish response to elevation in plasma urate in a patient with primary gout related to abnormal renal excretion of uric acid. Our laboratory has routinely analysed uric acid excretion in relation to rises in plasma urate induced by RNA administration to segregate those patients with primary gout who have impaired renal excretion of urate as the basis for their hyperuricaemia.

Fig. 1 Effect of rising plasma urate on urinary uric acid excretion in patient (●—●). For comparison the response of 10 normal subjects (○—○) and a single gouty underexcretor (□—□) to oral intake of 8 g RNA daily for 5 days is shown.

The case under study shows a markedly sensitive excretory response to rises in plasma urate concentration. For example, at a plasma urate level of 0.475 mmol/l, the uv urate per nephron unit was 169 nmol/min. The urate clearance was 33.4 ml/min at this plasma level, corresponding to 35.5% of the filtered load. A sustained plasma urate level of 0.475 mmol/l would result in a 24-hour urinary excretion of 22.9 mmol of uric acid.

The extent of proximal reabsorption of filtered urate was studied by inhibiting tubular secretion after oral administration of 4 g pyrazinamide. Two studies were performed, one at the endogenous plasma urate level, and the other after urate homeostasis had been obtained on 16 g of RNA daily. In the first study (Fig. 2A) pyrazinamide decreased uric acid excretion from 2.72 μ mol/min to as low as 0.053 μ mol/min, while in the second study (Fig. 2B) uric acid excretion fell from 12.99 μ mol/min to 0.261 μ mol/min. A minimum of 99.8% of filtered urate was reabsorbed proximally in the tubule at her endogenous plasma urate level, and, even when the filtered load had quadrupled after RNA administration, 99.5% of filtered urate was reabsorbed. These data attest to the integrity of the proximal reabsorptive site.

Fig. 2 A: Pyrazinamide suppression of filtered urate at endogenous plasma urate level. B: Pyrazinamide suppression of filtered urate following 16 g RNA loading

Since uricosuric drugs block reabsorption of uric acid at the postsecretory site, the maximum uricosuric response must equal the minimum amount of uric acid secreted. The patient's response to 80 mg micronised benzbromarone, a potent uricosuric drug, was studied at her endogenous plasma urate level as well as after raising it by RNA administration. The results of 5 representative studies are shown in Fig. 3, which compares her responses to that observed in normal subjects and gouty patients with overproduction of uric acid (cf. Fig. 4, Levinson and Sorensen, 1979). At all plasma urate levels studied the actual increment in urinary uric acid following benzbromarone administration was below that seen for the control group. At a plasma urate concentration of 0.48 mmol/l benzbromarone raised $\dot{V}$ urate from 35.5 ml/min to just 49.2 ml/min. Normally this dose of benzbromarone would increase uric acid clearance by some 400%. However, at the time of maximum uricosuria, urinary uric acid was similar in our patient and in the control group, suggesting that over a wide range of plasma urate concentrations the secretory response is quantitatively intact. The difference between the values for secretion and excretion of uric acid represents urate that has undergone reabsorption at the postsecretory site. In the present case reabsorption at the postsecretory site was significantly less than normal. This was especially noticeable when tubular secretion was enhanced after RNA administration. For example, at plasma urate concentrations between 0.4 and 0.5 mmol/l, postsecretory reabsorption of urate amounted to only one-third of that observed normally.

Fig. 3 Baseline urate excretion (●—●) and uricosuric response to benzbromarone (○---○) in the patient at endogenous urate level, and during RNA loading. Data are superimposed on 95% prediction bands showing urate excretion and uricosuric response to benzbromarone as a function of plasma urate in 8 normal subjects and 3 gouty overproducers (cf. Fig. 4, Levinson and Sorensen, 1979).

Discussion

We have reported on a 26-year-old woman who was found to have hyperuricosuria and an increased clearance of uric acid on RNA feeding while participating as a subject in a control study. No other metabolic or renal tubular abnormalities could be detected. In an attempt to determine the site of the renal abnormality resulting in increased clearance of uric acid, tubular reabsorption and secretion of uric acid were examined by studying the response to pyrazinamide and benzbromarone. The interpretation of the data is based on the assumptions that pyrazinamide in the applied dosage causes selective and complete blockage of secretion at a site distal to the nephron segment where filtered uric acid is reabsorbed and that benzbromarone results in virtually complete inhibition of reabsorption of secreted urate. Although the validity of both assumptions may be questioned, pyrazinamide and benzbromarone represent the most sensitive tools available at present for the pharmacological characterisation of renal transport of urate. The marked suppression of uric acid excretion by the patient after pyrazinamide indicates that proximal reabsorption of uric acid is not impaired.

Benzbromarone is not excreted by a renal tubular organic acid transport mechanism and does not interfere with tubular secretion of uric acid. The increment in urinary uric acid produced by a maximally effective dose of benzbromarone represents secreted urate that has been reabsorbed at the postsecretory site. The markedly reduced uricosuric response observed in this patient points to a decreased capacity for urate reabsorption at the distal locus as the underlying defect responsible for increased clearance of uric acid. No family members were available for study and it was not possible, therefore, to assess whether this defect was genetically determined. To our knowledge this is the first report of an isolated defect in urate reabsorption involving exclusively the postsecretory reabsorptive site.

As mentioned in the introduction, a postsecretory defect exists in some patients with Wilson's disease (Wilson and Goldstein, 1973) and in Hodgkin's disease (Bennett *et al.*, 1972). When these patients were given pyrazinamide, the urine became virtually free of uric acid. As regards the response to benzbromarone, the present patient responded like patients with Wilson's disease who have reduced uricosuric response to probenecid (Bearn *et al.*, 1957). The capacity of probenecid to increase the ratio $\dot{V}$ urate to $\dot{V}$ insulin was found to diminish as the tubular transport systems for urate deteriorated with progression of the disease.

Three different varieties of deficient tubular

reabsorption of urate have been described. In addition to the defect in postsecretory reabsorption of uric acid reported here a second defect involves diminished reabsorption of the filtered urate (Greene *et al.*, 1972; Sperling *et al.*, 1974; Benjamin *et al.*, 1977), while the third is a more severe defect characterised by profound hypouricaemia and a urate clearance in excess of the glomerular filtration rate (Praetorius and Kirk, 1950; Khachadurian and Arslanian, 1973; Simkin *et al.*, 1974). This defect appears to be related to deficient reabsorption of uric acid throughout the nephron. These experiments of nature, in conjunction with studies utilising pharmacological manipulations, serve to support the 4-component model for handling of uric acid in man.

This work was partly supported by grant 683-F9022 from the Illinois Chapter of the Arthritis Foundation.

The authors are grateful to Ms Orneary Rogers for preparing the manuscript.

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