Renal Tubular Regulation of Urea Excretion in Man

HERSCHEL V. MURDAUGH, JR., BODIL SCHMIDT-NIELSEN, ELEANOR M. DOYLE AND ROBERTA O'DELL. From the Departments of Medicine and Zoology, Duke University, and the Medical Service, Durham VA Hospital, Durham, North Carolina

Abstract

MURDAUGH, HERSCHEL V., JR., BODIL SCHMIDT-NIELSEN, ELEANOR M. DOYLE AND ROBERTA O'DELL. Renal tubular regulation of urea excretion in man. J. Appl. Physiol. 13(2): 263-268. 1958.—Adult male subjects were studied on a normal protein diet and on a low protein diet (basic rice diet with salt and fat supplements). Simultaneous inulin and urea clearances and total solute excretion were determined at high and low rates of urine flow on both diets. The glomerular filtration rate (GFR) was not altered by the low protein intake with salt added to the diet. After 5 weeks of low protein intake there was a marked decrease in the fraction of filtered urea excreted at low urine flows. This difference was not apparent during maximal water diuresis (inulin U/P < 15). At lower rates of urine flow (inulin U/P > 15) the fraction of filtered urea excreted at any given rate of urine flow was less than that found during normal protein intake. This difference increased at progressively lower rates of urine flow. The decrease in the fraction of filtered urea excreted during low protein intake was apparently not caused by changes in the rate of urine flow, GFR, plasma urea concentration, or total solute excretion. These findings indicate renal tubular regulation of urea excretion in man of a nature similar to that found in other mammals.

It has been demonstrated in kangaroo rats (1), white rats (2), camels (3) and in sheep (4, 5) that the urea clearance varies with the protein content of the diet. Furthermore, it has been found in camels and sheep that the change cannot be related to changes in glomerular filtration rate (GFR), plasma urea concentration, or osmotic load. These observations, therefore, show that the renal excretion of urea is regulated on the tubular level. According to the accepted concept for urea excretion in mammals, tubular regulation is not supposed to occur and it is assumed that urea is excreted by a mechanism of filtration and passive diffusion alone (6). The results mentioned above are thus in disagreement with the accepted concept. In spite of the commonly accepted view, the existing literature contains some evidence supporting the existence of renal tubular regulation of urea excretion also in man (7). However, the findings have not been conclusive and it seemed desirable to study the effects of altered protein intake more closely.

Methods

The subjects were men between 20 and 50 years of age. Eight of these were volunteer house staff physicians and three were hospital patients with no evidence of renal disease. The two diets, prepared by the hospital dietetic service, were: a normal hospital house staff diet with a protein content of 25% (150 gm protein, 3000 cal.), and a low protein diet with a protein content of 4% (25 gm protein, 3000 cal.).
Means of all determinations of GFR for the 6 subjects studied on both diets. There is no statistically significant difference between GFR on the 2 diets as evidenced by P value. Value for P determined by sum of squares (13). P > 0.4.

* Patient.

The latter was a Kempner rice diet modified by the addition of salt and fat. Five grams of salt were added daily to the 4% protein diet to approximate the salt content of the normal diet, in an attempt to prevent a decrease in GFR. The fat was added to make the caloric intake more nearly equal to the caloric intake of the 25% protein diet.

While the subjects were maintained on the normal diet a series of clearance studies was performed. The simultaneous urea and inulin clearances and total solute excretion were determined for each individual subject over the entire attainable range of urine flows, from maximal water diuresis to a minimum urine flow. The diet was then changed to the low protein diet and, after a period of at least 5 weeks, clearance experiments were again performed. Only six of the subjects studied remained on the administered diet without altering it for the entire period of study. Therefore, there were only six subjects studied on the low protein diet. Another subject remained on the diet but received gelatin supplements and was not considered as a low protein diet subject in the data.

All clearance determinations were started 6 hours postprandial, with the subjects in either a water loaded or a water deprived state. Urine collections were obtained by indwelling urethral catheter or by free voiding at 30- and 60-minute intervals. The collections of urine by free voiding would decrease the accuracy of the GFR determinations in individual collection periods; however, the mean GFR for the 6-8-hour period of study with a constant infusion of inulin should represent the true GFR for the period of study.

Urea and ammonia determinations were carried out using the microdiffusion technique of Conway (8). The true urea concentration was calculated as the difference between the total titer (urea + ammonia) and the titer for ammonia. The ammonia concentrations of all urine samples were consistently low and are therefore not shown in the tables. Determinations for inulin were performed by the resorcinol method of Roe as modified by Schreiner (9) and by the method of West and Rapoport (10). In several instances all analytical determinations were duplicated in two different laboratories. The determinations of urea and inulin by the two laboratories agreed within reported limitations of the methods. Osmolalities were determined using a Fiske Osmometer, model B.

RESULTS

Effect of Diet. Previous investigators have reported that a low nitrogen intake in itself does not cause a significant decrease in the GFR (11), while others report a slight but statistically significant decrease in GFR (12). In the present study the decreased protein intake with salt supplement was not associated...
Table 2. Data for urine collections at rates of urine flow of 1.6 ml/min. or less on all subjects studied on 2 diets

<table>
<thead>
<tr>
<th>Protein in Diet %</th>
<th>No. of Samples</th>
<th>Mean GFR ml/min.</th>
<th>Mean Tot. Solute Excretion mOsm/min.</th>
<th>Mean Urine Flow ml/min.</th>
<th>Mean Inulin U/P</th>
<th>Fract. Filtered Urea Excret.</th>
<th>Mean Plasma Urea mg %</th>
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</thead>
<tbody>
<tr>
<td>Subject A</td>
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<td></td>
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<tr>
<td>25</td>
<td>1</td>
<td>114</td>
<td>0.58</td>
<td>0.94</td>
<td>121</td>
<td>0.501</td>
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</tr>
<tr>
<td>25</td>
<td>2</td>
<td>115</td>
<td>0.52-0.60</td>
<td>0.49-0.59</td>
<td>182-240</td>
<td>0.276-0.329</td>
<td>42.0</td>
</tr>
<tr>
<td>25</td>
<td>4</td>
<td>114</td>
<td>0.24-0.29</td>
<td>0.28-0.38</td>
<td>238-354</td>
<td>0.008-0.207</td>
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<tr>
<td>Subject B</td>
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</tr>
<tr>
<td>25</td>
<td>3</td>
<td>95</td>
<td>0.43-0.78</td>
<td>0.70-1.41</td>
<td>83-165</td>
<td>0.341-0.470</td>
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<td>25</td>
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<td>0.30-0.55</td>
<td>0.55-0.70</td>
<td>182-242</td>
<td>0.325-0.459</td>
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<tr>
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<td>3</td>
<td>95</td>
<td>0.25-0.52</td>
<td>0.48-1.40</td>
<td>77-157</td>
<td>0.182-0.314</td>
<td>0.4</td>
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<td>Subject C</td>
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<tr>
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<td>3</td>
<td>131</td>
<td>0.29-0.60</td>
<td>0.48-0.67</td>
<td>110-206</td>
<td>0.190-0.320</td>
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<td>94</td>
<td>0.37-0.52</td>
<td>0.62-1.60</td>
<td>72-114</td>
<td>0.307-0.449</td>
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<td>8</td>
<td>127</td>
<td>0.51-1.09</td>
<td>0.45-0.95</td>
<td>138-253</td>
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<td>99</td>
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<td>0.20-0.46</td>
<td>245-404</td>
<td>0.063-0.106</td>
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<td>5</td>
<td>80</td>
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<td>0.30-0.39</td>
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<tr>
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<td>0.26-0.38</td>
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<tr>
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<td>142-154</td>
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<tr>
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<td>56</td>
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<td>0.21-0.31</td>
<td>214-354</td>
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<td>0.28-0.54</td>
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<td>0.125-0.127</td>
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<tr>
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<td></td>
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<tr>
<td>25</td>
<td>1</td>
<td>98</td>
<td>0.52</td>
<td>1.00</td>
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<tr>
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<tr>
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<td>1.10-1.38</td>
<td>45-50</td>
<td>0.500-0.590</td>
<td>18.0</td>
</tr>
</tbody>
</table>

The fraction of filtered urea excreted (the urea clearance/inulin clearance ratio) decreased markedly on the low protein regimen (fig. 2). This decrease is most apparent in the low ranges of urine flow. At higher urine flows the difference between the curves obtained on the two diets is less conspicuous. At extreme water diuresis (inulin U/P ratio 10-15) the data obtained on the two diets overlap completely.

The degree to which the kidney concentrates urea over the urea concentration of the plasma is lowered considerably on the low protein diet (fig. 3). During normal protein intake a maximum urea U/P ratio of approximately 100 is reached at inulin U/P ratios of 250-300. During low protein intake a maximum urea concentration decreases to approximately half its value on the normal diet (fig. 1). After this it remained relatively constant as long as the low protein diet was continued. In subject L (table 2), the plasma urea concentration was not decreased after 5 weeks of low protein intake, when the clearance studies were performed. (in this instance weekly determinations of plasma urea were not performed).
FIG. 2. Effect of diet and urine flow upon fraction of filtered urea excreted in the urine. Data are from 11 subjects on 25% protein intake and from 6 of these who remained on 4% protein intake. Data obtained on rising urine flow are not included to avoid exaltation (6). Data for subject D are not included (see text). Line on the graph is from data of Chasis and Smith obtained on normal protein diet (14). Statistical analysis by sum of squares showed that fraction of filtered urea excreted on the 2 diets was not significantly different for inulin U/P ratios < 10 (P > 0.8), but in range of inulin U/P ratios of 15–200 there was a difference in fraction of filtered urea excreted which was highly significant (P < 0.001). Analysis by linear regression gave similar results (13).

FIG. 3. Same data as in fig. 2 plotted as urea U/P ratios against inulin U/P ratios on a log. X log. scale. On low protein diet urea U/P ratios do not increase any further after inulin U/P ratios have reached a value of 100–150.

U/P ratio of about 40 is reached at inulin U/P ratio of between 60–100, but there is no further increase in urea U/P with increase in the inulin U/P ratio to as high as 600–800.

The observed decrease in the fraction of filtered urea excreted is not easily attributable to changes in plasma urea concentration. This is seen from the findings in subjects L and D (table 2). In subject L the fraction of filtered urea excreted decreased even though the plasma urea concentration was not decreased. Conversely, in subject D, the plasma urea concentration decreased after a period on the low protein diet and remained low while he was given 10–15 gm of gelatin daily during the week the clearance studies were performed and the fraction of filtered urea excreted did not decrease (table 2).

The total solute excretion, in general, was decreased during the low protein intake. This was to be expected with the decreased urea excretion. In some subjects, however, the total solute excretion during the clearance studies on low protein intake was of the same magnitude as found in the same subjects during normal protein intake. This was most likely a result of the salt supplement received during the low protein intake. The fraction of filtered urea excreted was not dependent upon the total solute excretion, since it decreased during low protein intake even if the total solute excretion was not decreased (table 2).

Acute Effect of Nitrogen Load. In order to study the effect upon the urea clearance of an acute nitrogen load, a few preliminary experiments were carried out in which protein or urea was administered to experimental subjects in the course of a clearance experiment. Two hospital patients were used as subjects. Subject L was maintained on a low protein intake. The effect of protein administration in the form of gelatin or egg albumin was studied in three different experiments. Subject F was maintained on a normal diet. This subject had no evidence of renal disease, but his GFR was only 50% of the normal rate for his body size. The effect of urea administration was studied in two experiments.

In both subjects the acute nitrogen administration caused the urea clearance/inulin clear-
The amount of urinary nitrogen excreted on a Kempner rice diet when nitrogen balance is reached is as low as 2.2 gm/day, while the amount excreted on a normal diet is about 15 gm/day. The urea nitrogen excretion decreases at the same time from 12 to 1.1 gm (or from 25.8 to 2.3 gm urea) per day (15). According to Kempner's observations, nitrogen balance is attained by the patients about 1-2 months after the dietary restrictions are instituted. In our experimental subjects the total nitrogen excretion was not determined, but it is reasonable to assume that nitrogen balance had been attained at the time of the repeat clearance studies since these were done 5-7 weeks after the dietary change.

A reduction in the fraction of filtered urea excreted could, theoretically, be attributed to a decrease in the GFR, a decrease in the plasma urea concentration, or a decrease in the solute load. This could be the case if a lowering in GFR or solute load prolonged the time the tubular fluid remained in the tubule and thereby caused an increase in back diffusion of urea.

Experimental evidence makes it unlikely that a lowering of GFR lowers the fraction of filtered urea excreted. Chasis and Smith (14), investigating patients with GFR ranging from 20% to 80% of normal, found that the fraction of filtered urea excreted was the same as in normal subjects. The same observation was made in dogs by Shannon (16). In patients on the Kempner rice diet the GFR decreases about 30%, but if salt is added to the diet the decrease in the GFR caused by the diet becomes minimal (11). In our subjects the change in diet had no significant effect upon GFR. In some subjects the GFR increased and in others it decreased slightly. The changes found in the fraction of filtered urea excreted thus were not produced by changes in GFR.

Plasma urea concentration did not appear to be the determining factor in the changes found in the fraction of filtered urea excreted. This is evidenced by the facts that the fraction of filtered urea excreted decreased in subject L, in whom plasma urea concentration was not decreased and did not change in subject D, in whom plasma urea concentration was decreased (but who received a gelatin supplement). These findings are similar to the findings in dogs (Schmidt-Nielsen, Murdaugh and O'Dell, in preparation), where a decreased fraction of filtered urea excreted was found at plasma urea concentration of 12.0 mg %, but not at plasma levels of 1.2 mg %. Ruminants (sheep and camels) could maintain a decreased fraction of filtered urea excreted during low protein intake, even when the plasma urea concentration was increased to the level observed on a normal protein diet (3, 5).

The total solute excretion did not correlate with the fraction of filtered urea excreted. In some subjects the expected decrease in total solute excretion on low protein intake occurred. In others, however, the total solute...
excretion during the clearance studies on the low protein diet was as high as that found during normal protein intake. (This presumably indicates that the salt supplement in these subjects was more than adequate.) Even if the total solute excretion was not decreased, the fraction of filtered urea excreted was decreased. Consequently, the decrease in the fraction of filtered urea excreted did not result from a decrease in the solute load.

It is thus apparent that there occurred a decrease in the fraction of filtered urea excreted on low protein intake which did not appear to be caused by changes in urine flow, GFR, plasma urea concentration, or total solute excretion. It is reasonable to conclude that this change was produced by a function of the renal tubules.

The nature of this regulatory mechanism cannot be ascertained on the basis of the present material alone. The finding that the difference in fraction of filtered urea excreted on the two diets is more pronounced at low urine flows and disappears altogether at maximum water diuresis is qualitatively similar to the findings in dogs (Schmidt-Nielsen, Murdaugh and O'Dell, in preparation), camels (3) and sheep (4, 5). There is no reason to assume that the basic mechanisms for the renal excretion of urea in man is not similar to these other species.

On the basis of data obtained in camels, sheep, dogs and rodents and on the basis of analyses of kidney tissue, it has been suggested that the renal mechanism for concentrating urea in the urine is a regulated active process that involves the countercurrent principle (17). The data on man are in agreement with the same hypothesis.

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