Renal Regulation of Urea Excretion in Sheep

BODIL SCHMIDT-NIELSEN, HUMIO OSAKI, H. V. MURDAUGH, JR., AND ROBERTA O’DELL

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ABSTRACT

SCHMIDT-NIELSEN, BODIL, HUMIO OSAKI, H. V. MURDAUGH, JR. AND ROBERTA O’DELL. Renal regulation of urea excretion in sheep. Am. J. Physiol. 194(2): 221-228. 1958.—In order to elucidate the renal mechanism for the regulation of urea excretion the urea clearance and the GFR were studied in sheep during normal and low protein intake in a range of urine flows from extreme osmotic diuresis to minimal flows. Differences in the effects of osmotic and water diureses and the effects of abrupt changes in rate of urine flow were also studied. In sheep on normal protein intake the urea/inulin clearance ratio was constant in the range of urine flows corresponding to inulin U/P ratios from 10 to 500. On low protein intake the urea/inulin clearance ratio decreased markedly with decreasing urine flow. At extremely high urine flows no difference was found between the urea/inulin clearance ratios on different diets. Regulation was found to be independent of GFR, plasma urea concentration and osmotic load and must therefore be on the tubular level. Observations during abrupt changes in urine flow showed that the urea clearance is not only abnormally high during increasing flows but also abnormally low during a sudden decrease in flow. The first phenomenon is known as ‘exaltation,’ and we have termed the latter phenomenon ‘abatement.’ The data on exaltation and abatement and on the effects of urine flow are consistent with a previously suggested hypothesis that the excretion of urea in the mammalian kidney is brought about through a regulated active transport of urea, accentuated by a countercurrent multiplier system represented by Henle’s loops and vasa recta.

IT IS EVIDENT from findings in camels (1) and sheep (2) that the renal excretion of urea in these ruminants is a regulated process which is related, in some manner, to the protein metabolism. An attempt to elucidate the mechanism by which this regulation is brought about has been made by studying the urea clearance and the glomerular filtration rate during normal and low nitrogen intake in the range of urine flows from extreme osmotic diureses to minimal urine flows. Also the difference in the effects of osmotic and water diuresis, and the effect of abrupt changes in the rate of urine flow have been studied.

METHODS

Experimental animals, diets and analytical methods were the same as described in a previous paper (3). A total number of 21 inulin infusion studies were performed on the two sheep D and E, with an average of 10 clearance periods per experiment.

In addition to the infusion studies the urea/ETC (endogenous true creatinine) clearance ratio was determined from time to time in all four sheep A, B, D and E by taking simultaneous blood and urine samples. In the infusion experiments the sheep was standing in a canvas sling on a wheeled cart. The technique is similar to the one used in certain experiments with dogs by Berliner and Davidson (3). It has the advantage that the animal is standing on its feet and is comfortable in a natural position. It is restricted in its movements only by the canvas sling that keeps it from stepping off the table.
The bladder was catheterized with a Foley catheter size 16. Using a Bowman infusion pump, inulin in normal saline was infused continuously through a polyethylene tube inserted in a hind leg vein. In experiments with low diuresis the maintenance infusion rate was 0.6 ml/min. (15 mg inulin/min.). Extreme osmotic diuresis was induced by the infusion of 50 gm of mannitol/1000 ml of saline at a rate of 12.9 ml/min. Pitressin was administered in the amount of 40 µg/min. in the osmotic diuresis experiment. To induce water diuresis a 3% glucose solution was infused. It was assumed that the glucose Tm for the sheep is around 200 mg/min., therefore not more than 175 mg glucose (or 3.5 ml) were infused per minute. In order to increase the diuresis 2 ml of saline was infused along with the glucose solution. The urine was hypotonic and glucose-free under these conditions.

The normal procedure in most experiments was as follows: after a priming dose and 40-60 minutes of constant infusion, urine collections were started. The collection periods were usually one-half hour, but varied between 10 minutes and 1 hour in the various experiments according to urine flow. Blood was collected at 30-60-minute intervals from the jugular vein. When the effect of rising urine flow was studied, three or four control samples were collected prior to the infusion of mannitol or glucose solution. The infusion of mannitol or glucose was usually stopped before the end of the experiment so that the urine flow would be slowly decreasing in the later urine collection periods.

When the sheep had been in water diuresis it was observed that a very abrupt decrease in urine flow would occur if the sheep started ruminating or eating. Sometimes a decrease to about a tenth of the preceding urine flow could be brought about within 15 minutes after hay was given (as can be seen from the change in inulin U/P ratio in table 2B). Consequently, we utilized this method to study the effect of rapidly falling urine flows.

**RESULTS**

**Glomerular Filtration Rate at Normal and Low Protein Intake.** In order to interpret the effects of diet on the urea clearance it is necessary to know if the glomerular filtration rate changes with changes in the nitrogen intake. In a camel placed on a low protein intake the variations in the urea clearance followed the variations in the nitrogen intake while the filtration rate did not decrease unless the salt intake was also reduced (1).

In the sheep the sodium chloride intake was maintained as far as possible at the same level on the two diets (approximately 5 gm/day for a sheep weighing 25-30 kg). From table 1 it is seen that the filtration rate, measured as inulin or ETC clearance, was not significantly affected by the level of protein intake. The variations in the average filtration rates in the three or four control samples were collected prior to the infusion of mannitol or glucose solution. The infusion of mannitol or glucose was usually stopped before the end of the experiment so that the urine flow would be slowly decreasing in the later urine collection periods.

When the sheep had been in water diuresis it was observed that a very abrupt decrease in urine flow would occur if the sheep started ruminating or eating. Sometimes a decrease to about a tenth of the preceding urine flow could be brought about within 15 minutes after hay was given (as can be seen from the change in inulin U/P ratio in table 2B). Consequently, we utilized this method to study the effect of rapidly falling urine flows.

**Table 1**

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<tr>
<th>Sheep D, body weight, 30 kg</th>
<th>U/P Ratios</th>
<th>Clearances, ml/min.</th>
<th>Clearance Ratio ETC/Inulin</th>
<th>Plasma Urea Conc., mmole/l.</th>
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osmotic diuresis was induced, by the infusion of mannitol and 12.9 ml of saline/min., the filtration rate was usually found to be somewhat elevated (table 1: exp. 8, 17 and 20).

Since the glomerular filtration rate shows no consistent change with varying nitrogen content of the diet, the changes found in the fraction of filtered urea excreted and in the maximum urea U/P (figs. 1 and 2) cannot be attributed to variations in the filtration rate.

Comparison of Inulin and Endogenous True Creatinine (ETC) Clearance. The ETC clearance is convenient for measuring the glomerular filtration rate because it can be used without employing an infusion technique. However, the comparison between ETC and inulin clearance in various animals has given somewhat variable results. In some species the two clearances show rather good agreement (1, 4), in others the results have been more variable (5). In the present studies the inulin clearance has been used as a measure for filtration rate in practically all of the experiments but since under some circumstances it is useful to be able to measure the glomerular filtration rate without infusion, we made extensive comparisons between the two clearances.

The results presented in table 1 show no statistically significant difference between the ETC clearance and the inulin clearance and no consistent difference between the ETC/inulin clearance ratio during normal and during low protein intake.

From the results in the sheep it can be concluded that although there may be some differences between ETC and inulin clearances the agreement between the two clearances is quite satisfactory for the present purpose if the measurements are not made during rapidly changing urine flow.\(^4\)

Effect of Urine Flow. The effect of urine flow upon the urea clearance is of particular interest for the understanding of the mechanism for urea excretion.

In figures 1 and 2 data obtained from all four sheep are plotted. Included in the graphs are data obtained in the 21 experiments listed in table 1, as well as data obtained when urine and blood samples were taken without inulin infusion. All data have been included with the exception of periods of rising or rapidly falling urine flow. (These data are shown in figs. 4 and 5.) No distinction has been made between data obtained during osmotic and water diuresis (see later).

In sheep on a normal protein intake the rate of urine flow has very little effect upon the fraction of filtered urea excreted (urea/inulin clearance ratio). The fraction is between 40 and 50\% throughout the range of urine flows from below 0.1 up to 5 ml/min., i.e. inulin U/P ratios between 500 and 10. Thus, the urea U/P ratio continues to rise in proportion to the increase in inulin U/P ratio (fig. 2). At high urine flows (inulin U/P < 10), the urea/inulin clearance ratio increases toward unity (fig. 1).

The data obtained when the sheep were

\(^4\) An observation which deserves further investigation is that the ETC clearance also, in practically all of the experiments, showed a slight degree of exaltation and abatement in the clearance periods where these changes were observed in urea clearance. It was observed both during osmotic and water diuresis, during normal and low protein intake.
maintained on the low protein diet show a different relationship. The fraction of filtered urea excreted decreases steadily with decreasing urine flow (fig. 1). A maximum urea U/P ratio of about 5 to 7 is reached already at an inulin U/P ratio of about 15-20 (fig. 2).

At higher urine flows, there is no measurable difference in the urea/inulin clearance ratio on normal and on low protein diet. The difference begins when the inulin U/P ratio is about 15 and increases as the urine flow decreases.

Two sets of data fall between the two curves: a) data obtained while the sheep was on a protein free diet (○), and was not conserving urea to the maximum extent (●); and b) data obtained on sheep E while it was still on a normal protein intake but had been subjected to several experiments within 1 month, and a considerable number of blood samples had been taken from it (▲). It is seen that the curves fall together when the inulin U/P ratio is lower than 10 and fan out as the inulin U/P ratio increases. The relationship stems from the fact that the urea U/P ratios reach maximum values at different inulin U/P ratios (fig. 2).

**Plasma Urea Concentrations.** In previous papers it was shown that the plasma urea concentration has no direct influence upon the level of the urea clearance in the sheep (2) or in the camel (1). The same relationship is apparent from the values given in table 1. Although in general the plasma urea concentration was lower when the protein intake was low, there were instances during low protein intake when the plasma urea concentration was as high as 2-3 mM (exp. 5 and 7) and the urea clearance was at its minimal value. Conversely, there were instances during normal protein intake when the plasma urea was as low as 2-3 mM (exp. 3, 4 and 17) and the urea clearance was at a normal high level.

**Water Diuresis and Osmotic Diuresis.** The rate of flow in the proximal tubule supposedly varies with the solute load. Wesson (6) has pointed out that the reabsorption of urea in the proximal tubule should vary with the osmotic load presented to the tubule. Thus, if the solute load is high the increased rate of flow through the proximal tubule should lower the passive reabsorption of urea. Conversely, a low solute load should enhance the passive reabsorption. It was of interest therefore to study in detail the effect of water and osmotic diuresis on urea excretion.

In the experiments on normal protein intake no differences were found whatsoever between the data obtained on osmotic diuresis and water diuresis. During low protein intake a small difference was observed. This difference, if at all significant, was apparent only in a small range of urine flows between inulin U/P ratios of 7 and 15 (fig. 3). From the values of osmolal U/P and urea U/P ratios in table 1 it is clear that the osmotic load has very little if any effect upon the level of the urea clearance. (In fig. 1 no distinction has been made between the urea/inulin clearance ratios obtained at different osmolal U/P ratios because of complete overlapping of the data.)

**Exaltation and Abatement.** When the urea excretion is observed during rapidly rising urine flow the urea clearance usually is abnormally high relative to the filtration rate. The phenomenon has been observed in man, dog, rabbit and other mammals and has been called 'exaltation' (7-9). In the present studies exaltation was observed regularly. In addition to this we observed the counterpart of exaltation, i.e. a lowering of the urea clearance occurring during rapidly falling urine flow. We will call this phenomenon 'abatement.'

A depression of the urea clearance with
falling urine flow has only rarely been mentioned in the literature. Shannon (8) found it in his dog G. The explanation for the more frequent occurrence of abatement in our experiments can probably be sought in the fact that it was possible to produce a more abrupt drop in urine flow in the sheep than is normally found in other mammals under usual experimental conditions.

For the elucidation of the phenomenon of regulation of the urea excretion it was desirable to study exaltation and abatement in the sheep on different diets and during osmotic and water diuresis. In figures 4 and 5 it is seen that exaltation (△ and ▲) was observed both when the urine flow increased due to a water load, and when it increased due to a solute load. Exaltation occurred both during normal protein intake and when the sheep were conserving urea maximally. It is of particular interest that the urea U/P ratio, which on the low protein diet normally did not exceed 5–7, actually increased with the sudden increase in urine flow. The increase was so marked that the urea U/P ratio sometimes doubled or tripled, rising to values as high as 10–17 (table 2A). These data indicate that the distribution of urea in the kidney of a sheep conserving urea may be quite different from that of an animal during normal protein intake.

As mentioned under methods the urine flow can fall abruptly if the sheep starts eating. The sudden drop in urine flow resulted in abatement of the urea clearance (table 2). Abatement (▽ and ▼) was observed at normal protein intake (fig. 4) as well as at low protein intake (fig. 5). Until recently no satisfactory explanation had been given for the phenomenon of exaltation. However, Ulrich and Jarausch have found in experiments with dogs that the tissue water at the tip of the renal papilla had the same urea concentration as the urine (10). This was found both at high and at low urine flows. Through this observation exaltation and abatement may be explained in the following way: when the urine flow rises the urea concentration in the tissue of the papilla will decrease and urea will be washed out from the entire tissue water thus causing an excess amount of urea to appear in the urine. Conversely, a sudden decrease in urine flow will be followed by an increase in the urea concentration in the tissue of the papilla. The urea clearance measured during a sudden drop in urine flow should therefore exhibit a lowering of the urea clearance as it has been observed in the present study.

A treatment of the data obtained in the sheep shows that the explanation is reasonable also from a quantitative point of view. In table 2B data from one of the experiments are presented. It is seen that during the period of rising urine flow the amount of urea excreted increased from 105 to 142 μmole/min. When the urine flow again was stabilized an excess amount of about 2800 μM had been excreted. At the same time the urea concentration in the urine had dropped from 611 to 38 μM/ml. If we assume that the concentration of urea in the renal papilla was the same as that of the urine when the urine flow had stabilized we can estimate that the amount of renal tissue water, from which urea was given off, was: 2800 μM/611–38, or 4.9 ml. In other words the increased urea excretion during exaltation corresponds to 5 ml of water that has changed its urea concentration from 611 to 38 μM/ml. The approximate weight of the renal crest in the two kidneys of a sheep is 4–6 gm. This way of dealing with the problem is of course an oversimplification since the loss of urea from the tissue must take place over the entire gradient from cortex to papilla. The calculation does, however, show that the order of magnitude is reasonable. Similar calculations on exaltation.

![Figure 3. Effect of osmotic and of water diuresis on the 2 different diets. Data ▲ and ▼ indicate values for which the osmolal U/P < 1. Data ● and ▲ are values with osmolal U/P > 1.](http://ajplegacy.physiology.org/DownloadedFrom)
DISCUSSION

The urea clearance in the sheep has been found to vary with the protein intake and the rate of urine flow in a very specific manner. Variations in the urea clearance of a similar nature but less pronounced have been observed in other mammals also viz. man (10a), dog (manuscript in preparation by B. Schmidt-Nielsen, H. V. Murdaugh, Jr. and R. O'Dell.) and rodents (11).

The effect of diet on the urea clearance in the sheep cannot be attributed to changes in the glomerular filtration rate since no consistent difference in GFR was found at the different levels of protein intake. It is also impossible to attribute these variations to changes in plasma urea concentration, since as noted earlier (2) as well as in the present study the level of the urea clearance cannot be correlated to the plasma urea concentration. Neither can the rate of flow in the proximal tubule as determined by the solute load be held responsible for the difference in excretion pattern on the two diets since the solute load had little or no effect upon the urea excretion.

Consequently the results lead us to conclude that the regulation takes place on the tubular level (2). A tubular mechanism, conceivably, could operate either through changes in the permeability of the renal tubule to urea or through changes in an active transport mechanism.

If we should explain the effect of urine flow on the urea excretion in the sheep according to the permeability hypothesis the findings that the urea clearance does not change in the range of urine flows corresponding to an inulin U/P ratio between 10 and 400 lead us to conclude that the renal distal tubules in the sheep on a normal protein intake are virtually impermeable to urea.5 We must also conclude that these same tubules under the conditions when the sheep is conserving urea become so permeable to urea that equilibrium is almost reached between tubular fluid and surrounding plasma. Furthermore, although the curves found agree rather well with the theoretical curves calculated by Wesson (6), a serious objection can be made against this reasoning. Wesson's calculations are based on a number of

5 The deduction is based on the assumption made by Shannon (8) and Chasis and Smith (7), that the proximal tubule is more permeable to urea than the distal tubule, and that the two different slopes found when urea/inulin clearance ratio is plotted against the inulin U/P ratio on a logarithmic scale reflect the permeability coefficients of the 2 segments of the tubule.
assumptions, one being that the plasma concentration in the capillaries surrounding the tubules is equal to the plasma concentration in other parts of the body. The findings by Ullrich and Jarausch make it highly unlikely that this is the case. It is more likely that plasma as well as extracellular and intracellular water shows an increasing urea concentration from cortex to papilla and that no steep gradients across tubular membranes are found.

The circumstantial evidence (as discussed in detail by one of us (IZ), is more in favor of the active transport hypothesis. A new hypothesis has been suggested on the basis of a great variety of observations. The present data have contributed substantially to the general picture and are integrated in the above mentioned discussion (I2).

Briefly summarized, the hypothesis suggests that urea is concentrated in the renal papilla and consequently (through diffusion) in the urine. The concentration mechanism consists of an active tubular transport of urea against a relatively small gradient. This gradient is maintained and amplified through a counter-current exchange and multiplier system, consisting of the vasa recta and the loops of Henle.

Since all the curves for the urea clearance during different diets converge and finally merge with increasing urine flow the amount secreted must either be graded according to urine flow, or there are other reasons that the secreted urea does not appear in the urine at high urine flows.

We know from the work of Ullrich and Jarausch that the urea concentration gradient in the renal tissue decreases with increasing urine flow. Without further experimental data we cannot determine how this change in gradient with urine flow is brought about. In a very simplified form two possibilities can be stated: a) the gradient from cortex to papilla decreases because of an increase in the relative flow through the juxtamedullary nephrons and capillaries. A larger fraction of the urea secreted would then be carried away with the increased flow and would not contribute to the gradient and not appear in the urine. In support of this possibility can be mentioned that

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Figures in parentheses are ETC U/P ratios. Plus and minus indicate periods with increasing and falling urine flows, respectively.
direct observation of the renal papilla of the living rat has revealed that the flow through the vasa recta is considerably higher during high rates of urine flow than during low rates (Gottschalk, personal communication).

b) Instead of the previous, perhaps most likely, explanation we could assume that the combined flow through the juxtamedullary nephrons and capillaries remains unchanged but that the active transport necessary to set up the gradient is graded according to urine flow.

The finding of exaltation and abatement during normal protein intake is qualitatively and quantitatively in agreement with the counter-current multiplier hypothesis. The finding of exaltation during low protein diet is not completely explained, but it may, through further studies, contribute significantly to our understanding.

Conclusion. The renal regulation of the urea excretion in the sheep is independent of GFR, plasma urea concentration and osmotic load. It is concluded that the regulation is on the tubular level. The regulation could be brought about through a change in the tubular permeability to urea or through a change in an active urea transport. The data obtained on the effect of urine flow upon the urea excretion together with data on the distribution of urea in the renal tissue (10) make the first possibility highly unlikely. The data on exaltation and abatement and on the effects of urine flow are consistent with the hypothesis that the excretion of urea is brought about through a regulated active transport accentuated by a counter-current multiplier system (12).

REFERENCES