Pathways of urea transport in the mammalian kidney

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Urea is the chief end product of nitrogen metabolism in mammals. Most of the urea produced is excreted by the kidneys. Excretion of a large fraction of the urea filtered by the glomerulus is required to keep pace with the rate of hepatic urea production. Consequently, the maintenance of nitrogen balance depends on a sustained high rate of renal urea excretion. One factor that might challenge the ability of the kidney to maintain a high rate of urea excretion is the need to limit water excretion. Theoretically, an increase in water absorption along the nephron would be expected to increase luminal urea concentration and consequently increase the driving force for passive urea reabsorption. Indeed, as demonstrated originally by Shannon [1] and confirmed in many subsequent studies, the rate of urea excretion decreases when water excretion decreases. However, the decline in urea excretion is relatively modest, even when the rate of water excretion is very low. In Shannon's studies in dogs [1], when water diuresis was established (water excretion 5–10 percent of filtered load), urea excretion was about 60 percent of the filtered load. During antidiuresis, when water excretion was reduced by 95% or more (to less than 0.5 percent of the glomerular filtration rate), urea excretion fell only by 25 to 30% (to 40 to 45 percent of the filtered load).

Urea accounts for a major fraction of the osmolality of the urine. Generally, unless dietary protein intake is restricted, 30 to 60 percent of total solute excretion on a molar basis is accounted for by urea [2–4]. When water excretion is low, the urea concentration in the urine rises to very high levels, typically well above 1 molar. Because water reabsorption by the renal tubule occurs predominantly by osmosis, the high concentration of urea in the lumen of the renal tubule might be expected to retard water absorption by its osmotic effect, much like an osmotic diuretic. Yet, the kidney can absorb well over 99 percent of filtered water despite the continued excretion of large amounts of urea.

The foregoing observations raise two important issues concerning urea transport in the kidney: a) how the kidney maintains a high steady–state rate of urea excretion over widely varying rates of water excretion; and b) how high urea concentrations can be achieved in the urine without retarding water reabsorption from the renal tubule.

The answers derive from an important observation made originally by Ullrich and Jarausch in antidiuretic dogs [5]. They

found that urea accumulates to high concentrations in the inner medulla of the kidney. This finding has been confirmed many times in several mammalian species using tissue slice analysis techniques. Micropuncture measurements in vasa recta, thin limbs of Henle's loops, and collecting ducts of rodents have demonstrated high urea concentrations in these structures [6–12], supporting the conclusion that urea accumulates in all structures of the inner medulla including the inner medullary interstitium. In the following, we describe how urea accumulation in the inner medulla accounts for maintenance of a high rate of urea excretion independent of changes in water excretion and for the ability of the kidney to conserve water despite the osmotic effect of high urinary urea concentrations.

Maintenance of high rates of urea excretion

As discussed above, water excretion by the kidney varies over a broad range to maintain water balance. Water excretion is controlled largely through the regulation of water permeability in the collecting ducts by vasopressin. A relatively constant fraction of the filtered load of water is delivered to the collecting ducts, and a variable fraction is reabsorbed as a result of changes in water permeability. Absorption of water increases the luminal urea concentration which could in turn increase passive urea absorption. Therefore, changes in collecting duct water absorption could in theory alter urea reabsorption and hence urea excretion. The kidney avoids large changes in urea excretion in response to changes in collecting duct water absorption in three ways: 1) delivery of urea to the distal tubules and collecting ducts increases when water excretion decreases [13]. This is a consequence of increased recycling of urea. 2) The urea permeability (measured in isolated perfused tubules) is low in the early part of the collecting duct system, that is in cortical collecting ducts [14–16] and outer medullary collecting ducts (unpublished observations, M. Knepper). Hence, urea reabsorption in these segments is likely to be virtually zero regardless of the luminal urea concentration. 3) In the inner medullary collecting ducts, the permeability to urea is extremely high [17–19]. In this segment, the rate of urea reabsorption is stabilized against changes in luminal urea concentration because urea accumulates in the inner medullary interstitium. The concentration of urea in the inner medullary interstitium changes in parallel with its concentration in the inner medullary collecting ducts and final urine [5, 20]. Therefore, despite large changes in luminal urea concentration, the transepithelial concentration difference across the inner medullary collecting ducts changes very little. That is, the driving
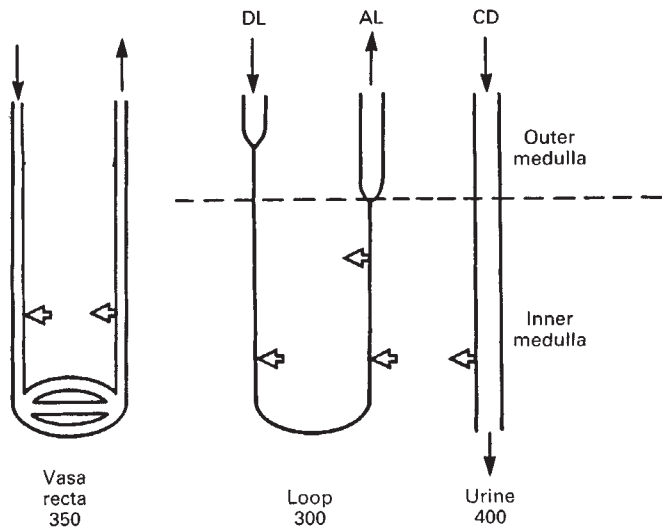
Fig. 1. *Orientation of concentration gradients driving passive urea transport in the inner medulla* (open arrows). Numbers indicate typical urea concentrations in vasa recta, at bend of loop of Henle and in collecting duct urine of nondiuretic rodents [9, 10]. Abbreviations are: DL, descending limb; AL, ascending limb; CD, collecting duct.

force for urea absorption is stabilized and consequently urea absorption is maintained relatively constant, independent of changes in water excretion.

Maintenance of renal tubular water absorption despite high urinary urea concentration

The question of how the kidney concentrates urea in the urine to such high levels without retarding water absorption from the medullary collecting ducts was answered by Berliner and his colleagues [21]. They pointed out that the high concentration of urea in the interstitium resulting from inner–medullary urea accumulation would balance the osmotic effect of the luminal urea in inner medullary collecting ducts. This would allow continued water absorption from the collecting ducts driven by the medullary sodium chloride gradient. Thus, urea accumulation in the inner medulla is critical to renal water conservation and, therefore, to the maintainance of systemic water balance.

As discussed above, accumulation of urea in the inner medulla is critical to the independent control of renal water and urea excretion. In the remainder of this paper, we address two important issues concerning urea accumulation in the renal medulla: 1) what are the routes of urea entry into the inner medullary interstitium that are responsible for urea accumulation; and 2) what mechanisms prevent or limit dissipation of the high urea concentration in the inner medulla.

Routes of urea entry into inner medullary interstitium

With two possible exceptions discussed below [7, 22], urea transport across renal epithelia is thought to occur by passive diffusion. Therefore, the possible sources of urea addition to the inner medullary interstitium can be identified by asking the question: where do transepithelial concentration gradients exist in vivo that favor passive diffusion of urea into the inner medullary interstitium? The answer to this question is summarized in Figure 1, in which the direction of urea concentration

gradients under normal nondiuretic conditions in rodents are indicated by open arrows oriented toward the lower concentration, that is, in the direction of passive diffusion. Among the renal tubule segments in the inner medulla, both inner medullary collecting ducts and the distal portions of the thin ascending limbs have concentration gradients which favor urea reabsorption. In addition, a concentration gradient exists between the urine present in the renal pelvis and the inner medullary interstitium that favors diffusion of urea across the papillary surface epithelium into the inner medulla (not shown in Figure). In the following, we discuss the relative quantitative importance of each of these epithelia in supplying urea to the inner medullary interstitium. The role of the vasa recta (the major blood vessels of the renal medulla), which remove urea from the inner medullary interstitium, will be discussed subsequently.

Inner medullary collecting duct

Klümper, Ullrich and Hilger [23] originally demonstrated by microcatheterization of the inner medullary collecting ducts of hamsters that substantial absorption of urea occurs from this segment. This observation has been subsequently confirmed in hamsters by micropuncture [24] and in rats by microcatheterization [25] and micropuncture [26]. The flux is large. Ten to 35 percent of the filtered load of urea is absorbed along the terminal part of the inner medullary collecting duct [23–26]. Consequently, it is generally accepted that absorption from the inner medullary collecting duct is a major source of urea to the inner medullary interstitium.

Under normal conditions, the urea concentration in the inner medullary collecting ducts is greater than in the vasa recta (and in the interstitium) [7, 10–12]. That is, there is a concentration gradient that favors passive urea absorption (Fig. 1). Direct in vitro measurements of urea permeability of the inner medullary collecting duct epithelium of rats and rabbits have revealed very high values, generally in excess of 10^{-4} cm/sec [17–19], supporting the conclusion that passive permeation can account for a major fraction of urea absorption from the inner medullary collecting duct. The inner medullary collecting duct is not uniform throughout its length with respect to urea permeability. The permeability is relatively low in initial third of the inner medullary collecting duct of the rat (2×10^{-5} cm/sec), but rises to 40 to 50 $\times 10^{-5}$ cm/sec in the middle and papillary thirds [19]. This allows passive urea reabsorption to be delayed to the deepest part of the inner medulla where the effective blood flow is lowest, thus maximizing urea accumulation near the papillary tip. Ullrich, Rumrich and Schmidt–Nielson [7] have suggested that absorption of urea from the inner medullary collecting duct may depend in part on an active process. Under some circumstances (such as low dietary protein intake), this may allow urea absorption to continue from the inner medullary collecting duct despite an unfavorable concentration gradient.

Papillary surface epithelium

Urine enters the renal pelvic space when it exits from the inner medullary collecting ducts at the papillary tip. Some of the urine refluxes backward over the outer surface of the papilla which is covered by a simple cuboidal epithelium, the papillary surface epithelium. Morphologically, this epithelium is similar (though not identical) to the inner medullary collecting duct [27, 28]. The urea concentration in the pelvic space is higher than in

the inner medullary interstitium. Thus, a concentration gradient is present across the papillary surface epithelium which could drive a passive flux of urea into the interstitium.

Marsh and Martin [24] measured the rate of urea absorption from the pelvic space indirectly by comparing the rate of delivery of urea to collecting ducts at the papillary tip with the delivery to the distal ureter. There was no difference in the urea delivery to the two sites, indicating that there was little if any loss of urea from the pelvic space. Supporting this conclusion, the papillary surface epithelium of the rabbit, isolated and mounted in a perfusion chamber, was found have a relatively low urea permeability, 1.2×10^{-5} cm/s [19]. This permeability is less than one–tenth the urea permeability of the rabbit inner medullary collecting duct at the same level of the inner medulla [19]. Experiments involving superfusion of the pelvic space with urea–containing solutions have shown that urea can penetrate the papillary surface epithelium given a long enough exposure time [29, 30]. However, Marsh and Martin [24] have pointed out that the urea flux in these experiments could have been dependent on the use of superfusion rates that were considerably higher than the flow of refluxed urine over the papillary surface epithelium. Taken together, the available evidence is consistent with the view that the pelvic space is not normally a major source of urea delivery to the inner medullary interstitium.

It should be emphasized that in many mammalian species, complex extensions of the renal pelvis (fornices) are present which allow pelvic urine to contact the outer surface of the outer medulla as well as the inner medulla. In fact, the fraction of renal pelvic surface area that contacts outer medulla greatly exceeds that which contacts the inner medulla in many species [31, 32]. Recent studies of the composition of the pelvic urine in rats indicate that urea loss from the pelvic space at the level of the deep pelvic fornices may significantly modify the pelvic urea concentration at that level [33]. That is, there may be transport of urea from the renal pelvis into the outer medulla. These studies, however, did not provide evidence of a significant rate of urea transport from the pelvic space at the level of the inner medulla.

Loop of Henle

The inner medullary portion of the long loop of Henle is made up of two morphologically–distinct segments: the thin descending limb and the thin ascending limb. We shall discuss them separately before considering the aggregate function of the long loops of Henle.

Thin descending limb. As the thin descending limb descends toward the papillary tip, it is exposed to increasing interstitial concentrations of urea. This tends to maintain a transepithelial urea concentration gradient that favors passive urea entry (Fig. 1). Such a gradient was directly demonstrated between vasa recta and thin descending limbs by micropuncture in hamsters [9]. Direct measurements demonstrated net entry of urea into the terminal portion of the hamster thin descending limb [9]. Thus, the thin descending limb does not appear to be a source of urea to the inner medullary interstitium, but rather appears to take up urea from the interstitium.

Thin ascending limb. In antidiuretic hamsters, urea entry into the initial part of the thin ascending limb was obseved [9], presumably because the concentration gradient that favors urea

entry into the thin descending limb is sustained in the initial portion of the ascending limb. Because the interstitial urea concentration falls steeply in the direction of the outer medulla, the direction of the transepithelial urea concentration gradient is likely to reverse in the late part of the thin ascending limb (Fig. 1). This would favor passive urea exit. The urea permeability of the thin ascending limb of the rabbit is very high (7×10^{-5} cm/sec [34]). The urea permeability is even higher in the thin ascending limb of the rat (23×10^{-5} cm/sec) and the hamster (19×10^{-5} cm/sec) [35]. Only one renal tubule segment has been found to have a higher urea permeability, the inner medullary collecting duct. The high permeability of the thin ascending limb presumably permits rapid equilibration of urea between the tubule fluid and the inner medullary interstitium. Thus, substantial efflux of urea from the late portion of the thin ascending limb is likely and the thin ascending limb probably supplies a considerable quantity of urea to the inner medullary interstitium.

Overall contribution of loop. Considered as a whole, the inner medullary portion of the loop of Henle may either supply urea to or remove urea from the inner medullary interstitium. The direction of net transport depends on the balance between passive urea secretion in the descending limb and early ascending limb, and passive urea reabsorption from the late ascending limb. The direction of transport cannot be resolved experimentally with present techniques since such a determination would require comparison of the mass flow rate of urea in the descending and ascending limbs at the inner–outer medullary border, which are inaccessible by micropuncture.

Mechanisms that limit dissipation of urea from the inner medulla

Countercurrent exchange

The blood that nourishes the inner medulla is carried into and out of the region by the vasa recta. *Descending vasa recta* descend from the cortex into the medulla and break up at various levels into the capillary plexuses that surround the renal tubules. The capillaries converge to form *ascending vasa recta* which ascend from the inner medulla toward the cortex. The descending and ascending vasa recta run in parallel, tightly associated in vascular bundles. Well–formed bundles are present only in the inner stripe of the outer medulla and the most superficial portion of the inner medulla [36]. However, the parallel relationship between the vasa recta is sustained throughout the inner medulla.

Close association of descending and ascending vasa recta facilitate countercurrent exchange of urea between the two structures which limits vascular washout of urea from the inner medulla [21]. The driving force for passive transport favors urea influx into the descending vasa recta as they descend in the direction of increasing interstitial urea concentration (Fig. 1). Conversely, the ascending vasa recta ascend in the direction of falling urea concentrations which promotes efflux of urea (Fig. 1). The permeability of the vasa recta to urea is extremely high ($>40 \times 10^{-5}$ cm/sec) [17]. As a result, there is rapid countercurrent exchange of urea from ascending to descending vasa recta. The concentration of urea in the ascending vasa recta exiting the inner medulla approaches the concentration in the descending vasa recta entering the inner medulla, minimizing

the washout of urea from the inner medulla. However, countercurrent exchange cannot entirely eliminate loss of urea from the inner medullary interstitium, even if complete equilibration occurs between the ascending vasa recta and the descending vasa recta. The reason is that under normal conditions, the volume flow rate of blood in the ascending vasa recta exceeds that in the descending vasa recta, owing to the continual addition of the water from the inner medullary interstitium. The added water derives from the inner medullary collecting ducts and descending limbs, both of which reabsorb water during antidiuresis. Because the mass flow rate of urea is equal to the product of the urea concentration and the volume flow rate, the higher volume flow rate in the ascending vasa recta will assure that the inner medullary vasculature continually removes urea from the inner medulla. Quantitatively, the most important loss of urea from the inner medullary interstitium occurs via the vasa recta.

The high urea permeability of the thin ascending limb allows this nephron segment to contribute to the countercurrent exchange process by permitting the urea concentration of the tubule fluid to equilibrate with that of the surrounding interstitium. This limits the amount of urea that exits the inner medulla in the ascending limb. It also contributes to the ultimate dilution of the tubule fluid exiting the thick ascending limb. In fact, because the luminal urea concentration near the bends of the loops can be greater than 300 mM [9, 10], urea must be absorbed at some site along the ascending limb to allow the osmolality of the luminal fluid exiting the thick ascending limb to fall below that of plasma as required for concentration of the urine [10, 11].

Urea recycling

Flow in the ascending limb of the loop of Henle and in the ascending vasa recta carries urea out of the inner medulla. Net loss of urea from the inner medulla via these two flows is minimized by countercurrent exchange as just discussed. An additional mechanism that conserves the urea accumulated in the inner medulla is *urea recycling*. Urea recycling returns to the inner medulla part of the urea that exits in the ascending vasa recta and ascending limb of Henle's loop. Three major urea recycling pathways (Fig. 2) are described in the following:

Recycling through the ascending limbs, distal tubules and collecting ducts (pathway a, Fig. 2). Some of the urea in the inner medullary interstitium enters the loop of Henle and exits the inner medulla via the thin ascending limb. A large fraction of the urea present in the thin ascending limb will remain in the lumen and be carried through the distal convoluted tubule and cortical collecting ducts and finally back to the inner medullary collecting ducts to complete the cycle [6].

Recycling through the vasa recta, short loops of Henle, and collecting ducts (pathway b, Fig. 2). In micropuncture studies of nondiuretic rats [6, 8, 37–40], the delivery of urea to the superficial distal tubule was found to exceed the delivery out of the superficial proximal tubule. That is, there is net urea addition along the short loops of Henle. To explain this observation, Valtin [41] proposed that urea exiting the inner medulla in the vasa recta enters the descending limbs of the short loops of Henle. The urea that enters the short loops is carried through the superficial distal tubules and back to the inner medulla via the collecting ducts, thus completing a recycling pathway.
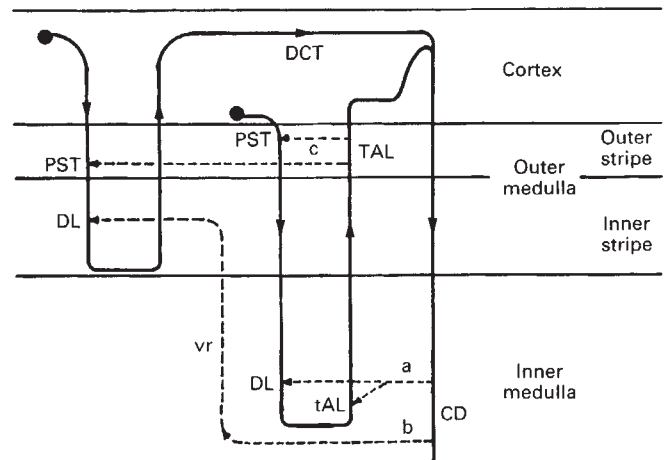

Fig. 2. *Pathways of urea recycling in the mammalian kidney.* Solid lines represent a short–looped nephron (left) and a long–looped nephron (right). Transfer of urea between nephron segments is indicated by dashed arrows labelled a, b, and c corresponding to recycling pathways described in text. Abbreviations are: PST, proximal straight tubule; DL, descending limb; tAL, thin ascending limb; TAL, thick ascending limb; DCT, distal convoluted tubule; CD, collecting duct; vr, vasa recta.

Preferential transfer of urea from the vasa recta to the short loops of Henle may be facilitated by a close physical association between these structures in the vascular bundles of the inner stripe of the outer medulla in some animal species [36].

Recycling between ascending limb and descending limb (pathway c, Fig. 2). Studies of isolated perfused thick ascending limbs have revealed important axial heterogeneity with regard to urea permeability [16, 42, 43]. Although the urea permeability of thick ascending limbs from the inner stripe of the outer medulla is too low to permit a substantial amount of urea absorption [16, 44], the permeability is considerably higher in segments from the outer stripe and medullary rays [16, 43]. Urea reabsorbed from these thick ascending limbs was proposed to enter neighboring proximal straight tubules completing a recycling pathway between the ascending limb and descending limbs of the loop [16, 42, 43]. This transfer is facilitated by the parallel relationship between thick ascending limbs and proximal straight tubules in the outer stripe and in the medullary rays, and may depend on a relatively attenuated effective blood flow in these regions. Secretion into the proximal straight tubules may occur by active transport [22], by passive diffusion [43], or by a combination of active and passive processes. The urea that enters proximal straight tubules of short looped nephrons will be carried back to the inner medulla by the flow of tubule fluid through the short loops of Henle, superficial distal tubules and collecting ducts. The urea that enters proximal straight tubules of long loops will be returned directly to the inner medulla via the descending limbs. This recycling pathway may be responsible in part for the very high fractional delivery of urea to the inner medullary thin descending limb of rats (>300% of filtered load) [10, 11], hamsters (>200%) [9], and psammomys (>150%) [12].

Conclusion

In the foregoing, we have emphasized the central role of inner medullary urea accumulation in the independent control of

renal urea and water excretion. We have described the sources of urea that are responsible for the high concentration of urea in the inner medulla, pointing out the predominance of urea absorption from the inner medullary collecting duct. We have described the processes that dissipate urea from the inner medulla, emphasizing the predominance of the vasa recta. Finally, we have discussed the mechanisms that limit dissipation of urea from the inner medulla: countercurrent exchange and urea recycling.

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