The urinary concentrating mechanism: 
 a model of integrative physiology

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Introduction

One of the most efficient water conservation mechanisms in mammals is the ability of the kidneys to produce concentrated urine for the elimination of waste products while losing a minimum of water. Depending on the food supply of differing animals, components of the glomerular ultrafiltrate are concentrated in the final urine to different extents. For example, carnivorous animals preferentially eliminate urea, the waste product of protein metabolism, whereas herbivores concentrate potassium but conserve urea as nitrogen source of protein synthesis, and marine mammals concentrate salt ingested from sea water. Thus, although there are differences in the underlying renal mechanisms, the general organization of these systems is similar in all mammals, including humans.

The urinary concentrating mechanism: general picture

In 1942, Kühn and Ryffel [1] first proposed that a small concentration difference between two compartments would be multiplied in a counter-current system if the membranes separating the compartments had the required permeabilities. Each mammalian nephron possesses a loop directing the fluid in two opposite directions (the descending and ascending limbs of Henle’s loop), creating a counter-current circulation in the kidney parenchyma. Together, these loops act as counter-current multipliers generating a cortico-medullary concentration gradient. This gradient is established primarily from the outward transport of NaCl, but not water, along the ascending limb of the loop. The NaCl leaving the ascending limb produces a hypertonic medullary interstitial space and dilutes the fluid remaining in the tubular lumen. These two consequences play a fundamental role in the concentrating process. First, the transport of hypertonic NaCl through the ascending limb creates a concentration difference between the tubular lumen (diluted) and the medullary interstitium (concentrated). This small difference is then multiplied by the counter-current circulation of the fluid in the loop, resulting in a progressive increase in osmotic pressure from the cortex (iso-osmotic to plasma) to the papillary tip. Second, the loop of Henle delivers a hypotonic fluid to the distal convoluted tubule.

In the presence of vasopressin, the distal convoluted tubules and the cortical and medullary collecting ducts become permeable to water. The hypotonic fluid circulating in the cortex equilibrates with the iso-osmotic interstitium by water withdrawal. Through this mechanism, the cortical collecting ducts deliver a reduced volume of iso-osmotic fluid to the medulla. In the medullary collecting duct, the same equilibration process continues. The osmotic pressure of the luminal fluid rises and the tubular flow rate declines as the fluid progresses along the collecting ducts and travels down the longitudinal concentration gradient. The concentration of final urine is, therefore, governed by the amplitude of the cortico-medullary concentration gradient.
Lights . . .

The functions of the tubular and vascular elements participating in the urinary concentrating mechanism and their interrelationships are incompletely understood.

The rat, an omnivorous animal, can be used as a model. Under normal conditions, the longitudinal concentration gradient results from parallel increases in NaCl and urea in the medulla [2].

Sodium handling is different in the two compartments of the medulla. In the outer medulla, the cells of the ascending limb are relatively wide and are equipped with the anatomical and biochemical characteristics of transporting epithelium. NaCl is transported from the lumen towards the interstitium through active or secondary active transporters. The molecule is then re-introduced into the descending limb through the NaCl-permeable epithelium of the thin descending limb of juxtamedullary (long-looped) nephrons. This type of sodium chloride recycling helps to maintain the cortico-medullary concentration gradient. In the inner medulla, the thin descending limb epithelium becomes impermeable to NaCl but remains permeable to water. A sodium-rich solution enters this segment, and NaCl continues to concentrate along the descending thin limb, by osmotic water removal into the solute-rich interstitium. A sodium-rich solution enters the water-impermeable, but sodium-permeable, thin ascending limb. As the fluid ascends this limb, it dilutes progressively by NaCl diffusion out of the tubule. At each level of the inner medulla, as in the outer medulla, a small concentration difference exists between the descending and ascending limbs, creating conditions required for the operation of a counter-current multiplier concentration system.

The diffusion of urea also contributes to a medullary recycling process. Intratubular urea, leaving the cortical collecting ducts, is progressively concentrated by osmotic water withdrawal as the fluid flows down the longitudinal concentration gradient along the urea-impermeable outer medullary collecting ducts and the two first segments of the inner medullary collecting ducts. A urea-rich solution, therefore, enters the last segments of the inner medullary collecting ducts, which in the presence of vasopressin, is highly permeable to urea. Urea diffuses massively into the interstitial space at the tip of the papilla, and this addition of urea adds to the hypertonicity of the inner medulla interstitium. Urea then leaves the inner medulla via the urea-permeable ascending vasa recta. In the outer medulla, the ascending vasa recta enters into contact with the urea-permeable thin descending limbs of the superficial (short-looped) nephrons. Urea enters the thin descending limbs, and flows down the urea impermeable segments to the end of the cortical collecting ducts. Therefore, an already urea-rich solution enters the medullary collecting ducts, and the urea concentration becomes amplified, as previously described, by osmotic withdrawal of water before reaching the inner medullary collecting duct at the tip of the papilla. The movements of sodium and urea in the medulla, schematically described here, are well established.

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What is unclear are the mechanisms (the forces) of water and solute transport in the medulla. In the outer medulla, experimental data indicate that NaCl is actively transported out of the thick ascending limb and that this is sufficient to account for the longitudinal NaCl gradient in this region. In addition, this transport concentrates urea in the outer medullary collecting duct through osmotic water withdrawal combined with the NaCl rich interstitium.

The mechanisms are different in the inner medulla. There is no evidence for active NaCl transport in the thin ascending limb of Henle despite the concentration difference between the thin ascending (diluted) and the thin descending limb solutes at each level of the inner medulla.

A ‘passive concentrating mechanism’ has been proposed [3] to explain the handling of NaCl and urea in the inner medulla. This mechanism was based on the urea and NaCl movements described previously. However, such a mechanism is unlikely for several reasons.

The theory in summary proposes that NaCl flowing to the tip of the papilla is progressively concentrated in the thin descending limb by osmotic water withdrawal; urea is also concentrated by water withdrawal in the first portions of the inner medullary collecting ducts. Thus, urea and NaCl account for the hypertonicity of the interstitium. In other words, the osmotic forces in the interstitial space necessary to increase the concentration of urea and NaCl in the descending structures are the consequences of this increase: the consequences are themselves the causes! In fact, whatever the permeability properties of the tubular and vascular components of the inner medulla, the maximal concentration attainable at the tip of the papilla is the same as can be reached at the base of the inner medulla. Such a passive mechanism cannot explain how the longitudinal concentration gradient continues to increase along the inner medulla axis.

In addition, computations with input parameters representative of experimentally measured values that were based on models similar to the passive concentrating mechanism model are incapable of predicting concentrations of solutes in the inner medulla in the absence of an active transport process [4,5].

Finally, in the passive concentrating mechanism model, urea transfers energy created by the active transport of NaCl (out of the thick ascending limb) from the outer to the inner medulla to concentrate the NaCl in the thin descending limb of juxtamedullary nephrons. This strongly indicates that the longitudinal gradients of urea and NaCl develop in parallel. However, this is not the case in the desert rodent, Psammomys obesus [2] (Figure 1). A discrepancy in
sodium and urea distribution was also reported by Schmidt-Nielsen and O’Dell [6] in sheep fed a low-protein diet (Figure 2). In sheep and in Psammomys (as well as in the rat fed a low-protein diet, see below), the delivery of urea from the outer medulla as an energy source to passively concentrate sodium, flowing down the thin descending limbs of long looped nephrons, in the inner medulla should create a positive correlation between the distribution of sodium and urea in the inner medullary tissue. A positive relationship is also expected between the sodium content of the thin descending limbs and the urea content in adjacent vasa recta because the vasa recta fluid theoretically reflects the composition of the interstitium.

**Advances and hopes**

Although molecular biology has provided some recent advances, there have been few new insights in our understanding of the countercurrent multiplier mechanism in the inner medulla.

However, a recent discovery provided an explanation for a long unresolved problem. In rats given a low-protein diet, the fractional excretion of urea is considerably reduced. In parallel, the longitudinal urea concentration profile is reversed. The maximum inner medullary urea concentration is found at the base and decreases towards the papillary tip. However, in the initial segment of the inner medullary collecting ducts (IMCD1) facing this region, urea is reabsorbed in spite of an unfavourable uphill concentration gradient. Although there has been a long-standing general agreement that urea is actively reabsorbed along this segment, 30 years of research has not demonstrated evidence of such a transport system. During the past 5 years, Jeff Sands and his group [7] demonstrated that feeding rats a low-protein diet for several weeks induced the expression of a secondary active, sodium-dependent urea transporter. In addition, active transport in IMCD1 segments was induced by manoeuvres that reduced urine concentrating abilities [8], such as hypercalcaemia. Surprisingly, water diuresis did not induce active reabsorption of urea in the IMCD1 segment, but induced active urea secretion in IMCD2 segments.

Nevertheless, significant progress has been made with molecular and cDNA cloning approaches. For example, we have increased our understanding of the renal distribution of aquaporins [9], better known as...
water channels, and urea transporters [10], and their regulation by hormones and diet. These data give a structural and molecular basis to the permeability changes and transport properties of the different nephron and vascular segments. Overall, the properties of recently identified and investigated gene products confirm the permeability properties of the vascular and tubular structures expected to contribute to the urinary concentrating process. They provide strong evidence that vasopressin-dependent permeabilities rely on the expression of specific molecules whose insertion into the plasma membrane of transporting cells vary with the level of circulating vasopressin. The main impact of these new investigative tools is probably their application to the human kidney. Research on microdissected kidney segments will open new fields of study in human physiology and pathophysiology. Such an approach will benefit from knowledge of the genome and from new tools allowing gene expression analysis at a global scale. The application of new findings derived from the unravelling of proteomes and transcriptomes to a given situation will allow the completion of integrative physiological or pathological studies. A more complete understanding of how this system works will probably have to wait until these methods are applied to the renal concentrating mechanism.

References

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