Glomerular protein separation as a mechanism for powering renal concentrating processes

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Abstract—Various models have been proposed to explain the urine concentrating mechanism in mammals, however uncertainty remains regarding the origin of the energy required for the production of concentrated urine. We propose a novel mechanism for concentrating urine. We postulate that the energy for the concentrating process is derived from the osmotic potentials generated by the separation of afferent blood into protein-rich efferent blood and protein-deplete filtrate. These two streams run in mutual juxtaposition along the length of the nephron and are thus suitably arranged to provide the osmotic potential to concentrate the urine. The proposed model is able to qualitatively explain the production of various urine concentrations under different clinical conditions. An approach to testing the feasibility of the hypothesis is proposed.

I. INTRODUCTION

The renal mechanism for concentrating the urine in mammals is incompletely understood and is widely believed to involve the presence of molecular pumps capable of pumping solutes against their concentration gradients [1]; a particularly energy-intensive process. Alternative explanations for the process have been proposed which do not invoke the concept of membrane pumps [1], however these so-called passive models do not provide an explanation for the origin of the energy in the concentrating process. Indeed, some authors even argue against the very existence of these energy-dependent pumps [2], [3]. For a model of the renal concentrating mechanism to be consistent, it would need to explain the observed urine concentrating phenomena and correctly predict what would happen under various clinical circumstances.

II. BACKGROUND

The primary functions of the kidney are ridding the body of nitrogenous metabolic waste products, maintaining an appropriate electrolyte balance, and ensuring the body’s water balance is maintained. This is achieved through the production of small volumes of concentrated urine during times of dehydration (anti-diuresis) and large volumes of dilute urine during times of over hydration (diuresis).

A. Macroscopic measurements

What is known and measurable at a macroscopic level is that metabolic waste-laden blood is delivered to the kidneys at mean arterial pressure via the renal arteries, and slightly “cleaner” blood is removed at central venous pressure via the renal veins. The waste products, excess solutes and water are removed from the kidneys in the form of urine. A cortico-medullary concentration gradient exists from the boundary between the cortex and medulla to the tip of the papilla and is present in the kidneys of all mammals [1], apparently maximised during anti-diuresis and reduced during diuresis [4], [5], [6]. Glomerular filtration rate (GFR) is the filtration rate of plasma in the kidney and is approximately 20% of renal plasma flow, averaging about 180 litre/day in healthy humans [7].

B. Microscopic structure

There are estimated to be between 0.3 and 1.4 million nephrons in the human kidney [8], specifically arranged with their various structural parts (renal corpuscle, proximal convoluted tubule, loop of Henle, distal convoluted tubule and collecting duct) and their closely associated blood supply in either the cortex or medulla. Peritubular capillaries surround the cortical structures while the vasa recta surround the medullary structures. This suggests structural and functional heterogeneity of the kidney [9].

C. Urine concentration

Urine varies in concentration according to the hydration state of the animal. At the extremes of over-hydration and dehydration, humans, for example, are said to be able to dilute their urine to approximately 1/6 the concentration of plasma and concentrate their urine to approximately 4 times the concentration of plasma, respectively [1], [7]. The associated volumes of urine vary from approximately 18 litres to 0.5 litre. Urea (the main nitrogenous waste in mammals) is water soluble and therefore requires a certain obligatory volume of water to be excreted along with it, thus limiting the concentrating ability [7]. Vascular flow within the medulla also has the effect of limiting urine concentrating ability because of its dissipative effect on the cortico-medullary concentration gradient [11], [7].

1) Traditional model: The traditional model of the urine concentrating process involves ultrafiltration of plasma at the glomerulus and subsequent reabsorption and secretion processes (some passive and others active) along the length of the nephron, ultimately yielding urine [1]. The explanation for the establishment of the cortico-medullary gradient is countercurrent multiplication of a so-called single effect which is a small osmotic pressure difference between flows in parallel ascending and descending tubules of the nephron [10]. In the outer medulla, the single effect is said to involve pumping sodium chloride out of the ascending limb of the loop of Henle, against its concentration gradient [11], [12], to provide the osmotic gradient to promote water movement out of the
descending limb and collecting duct and back into the blood. It has been shown that the single effect in the inner medulla is not due to sodium pumping and various hypotheses have been put forward to explain it, but none have been satisfactory.

2) Anti-diuretic hormone: Differential urine concentration is apparently mediated through the effect of Arginine Vasopressin or Anti-diuretic Hormone (ADH) on the kidney. During dehydration, high osmolality of the blood or low plasma volume causes ADH to be released from the posterior lobe of the pituitary, while during over-hydration, ADH is not released.

Tubular ADH receptors are located on the walls of the collecting duct and respond to ADH by increasing the collecting duct permeability to water. Water is then able to pass from the relatively dilute filtrate into the concentrated interstitium of the medulla and surrounding vasa recta, thereby being returned to the blood and conserved. In comparison, during over-hydration, the release of ADH is not stimulated and therefore the walls of the collecting ducts remain relatively impermeable to water and the dilute filtrate passes out of the kidney as dilute urine.

D. Energy considerations in the concentration of urine

In terms of fundamental thermodynamic principles, and as pointed out by others, to avoid violating the law of conservation of energy, the energy put into the system must account for the osmotic work performed in creating concentrated urine. The energy-intensive molecular pumps needed in the traditional model have been shown to require more energy than a cell has available to use. Therefore casting doubt on the thermodynamic integrity of the traditional model. A number of authors have considered the energy requirements of urine production; however, the source of the energy remains uncertain.

III. Hypothesis

In addition to requiring energy intensive molecular pumping of solutes against their concentration gradients, the traditional model of the urine concentrating mechanism appears to have ignored the osmotic effect of protein remaining in the efferent blood. We propose that the separation of afferent blood into filtrate, which is relatively protein-free, and efferent blood, which is more concentrated in serum protein than the afferent blood, by the process of ultrafiltration at the glomerulus, provides the chemical potential energy for all the remaining concentrating mechanisms in the tubules. We suggest that the overall urine concentrating mechanism in mammals may not require more energy than is provided at the initial separation step and that there is therefore no need to propose the molecular pumping of solutes.

IV. Proposed Model

The proposed model for the urine concentrating mechanism in mammals needs to explain how, in humans for example, 180 litre/day of filtrate (at almost plasma concentration of 290 mOsm/litre) is converted to 0.5 litre/day concentrated urine (at about four times plasma concentration) in the case of dehydration. The hypothesis must also be consistent with various known clinico-pathological conditions, in order to be considered a viable model worthy of further study.

We propose a model whereby the only energy input into the system is the energy of protein separation, which occurs during ultrafiltration at the glomerulus. The energy for ultrafiltration is derived from the hydrostatic pressure originating in the cardiovascular system. Osmotic separations constitute real and usable stored energy, and mixing may be used to recover this energy as work. Indeed, industrial-scale osmotic energy storage and harvesting are being tested.

If the energy of separation at the glomerulus exceeds the energy required to concentrate urine, then it may be concluded that an external energy source, such as energy-intensive molecular pumping in the traditional model, is not needed, and that the proposed model, at a high level, is thermodynamically viable.

A typical nephron has been redrawn as a high level compartment model in figure. Afferent blood originating from the renal artery enters the first blood chamber (i.e. representing the glomerular capillary network in the Bowman’s capsule) and a portion is filtered (approximately 20%) across the membrane due to the net pressure difference (hydrostatic and oncotic) of approximately 10 mmHg. The resulting filtrate resembles plasma in composition but without serum proteins (i.e. the membrane is permeable to small solutes but not to larger negatively-charged protein molecules), while the efferent blood is simply lacking a portion of plasma and is therefore concentrated (by 20%) in serum protein. Albumin has a complex non-linear behaviour in terms of its osmotic coefficient and when concentrated, it appears to be substantially more osmotically active.

The oncotic pressure in the efferent blood may thus be far greater that the simple 20% increase in concentration would imply. The filtrate resides in the filtrate compartment (i.e. within the nephron tubule lumen), and is able to interact osmotically with the efferent blood in the second blood chamber (i.e. peritubular capillaries in the cortex or vasa recta in the medulla), separated by the nephron membrane that may be differentially permeable to different solutes. If the energy of separation is sufficient to concentrate urine, then the separation process can be thought of as a battery being charged up. The potential energy stored in this osmotic battery is then drawn down to run the more distal concentrating processes. Once the filtrate has traversed the length of the nephron, it leaves its compartment via the ureter as urine, while the efferent blood is returned to general circulation via the renal vein.
V. Predictions and Justification

The normal urine concentrating process can be qualitatively explained by the model proposed in this paper. During dehydration, the model predicts concentrated urine production, mediated by ADH secretion. Tubular receptors change the water permeability of the nephron membrane (i.e., reducing resistance to water flow from the filtrate compartment into the efferent blood compartment), causing more water to be reabsorbed and urine to be concentrated. As long as the energy of separation exceeds the energy needed to concentrate the urine, changes in membrane permeability due to the effect of ADH secretion should be sufficient to explain the increased urine concentration.

The fact that newborn mammals and birds cannot create concentrated urine [27], [28], [29], [30], [31] is typically explained by immaturity of the organ [1]. However, it has also been found that infants have low serum protein levels relative to adult values [32], [33]. This finding fits with our hypothesis that low serum protein levels reduce the ability of the kidneys to provide the necessary chemical potential energy for concentrated urine to be produced.

A clinical observation that can be explained by the proposed model, and not by traditional models, is that of renal failure following hepatic failure. The pathogenesis of this so-called hepato-renal syndrome is unclear, and there is no visible renal histopathology [34], [35]. Furthermore, administration of albumin appears to be renoprotective in this condition [36] and renal function typically resumes after successful liver transplantation [37], [38]. We suggest that our hypothesis explains these findings on the grounds of hypoalbuminemia accompanying liver failure [1]. According to our hypothesis, a reduction in serum protein level would mean a reduced ability to set up the chemical potential to drive the tubular processes, resulting in renal failure. Similarly, an increase in serum protein level following liver transplantation or albumin administration would provide the chemical potential necessary for urine concentration and improved kidney function.

Finally, this model would suggest that severe proteinuria may result in diminished renal function because the presence of protein in the filtrate represents inadequate separation at the glomeruli, and thus less osmotic potential for the distal processes. The association between proteinuria and diminishing renal function has been described but the mechanism remains unclear [39], [40].

VI. Conclusion

The proposed model is simple in its conception and in its current, qualitative state, it is able to provide a qualitative explanation for the observed phenomena in urine concentration and predict what happens under certain pathological conditions. The next step is to quantify the model parameters, run simulations to test the model and ultimately determine whether the hypothesis could be valid. As with any scientific hypothesis, falsifiability is an important and necessary feature [41]. We propose that this can be achieved thorough a quantitative thermodynamics analysis of the energy balances in the proposed process.

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