Renal tubular disorders

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Abstract

Renal tubular disorders are challenging and comprise a heterogeneous group of disorders. This review concentrates on those presenting in childhood with electrolyte abnormalities. Pattern recognition of these abnormalities is important in making diagnoses and a basic understanding of renal tubular physiology is helpful to understand why these patterns occur.

Clinical cases are used as illustrations in this review, supported by physiological descriptions of the disorders and notes about their management.

Although these disorders almost invariably come under the long-term management of paediatric nephrologists, they will just as invariably present to general paediatricians. This review should equip general paediatricians with the skills to request the appropriate initial investigations to make the correct diagnosis. There is also some advice on when to suspect a diagnosis of a renal tubular disorder and how to spot a child with a genuine polydipsia.

Keywords Bartter's; cystinosis; diabetes insipidus; Fanconi; Gitelman's; polydipsia; polyuria; pseudohypoaldosteronism; renal tubular acidosis; renal tubular disorder; tubulopathy

Introduction

Tubular disorders are the extra-virgin product in a Marmite paediatric subspecialty! The trainee, celebrating their MRCPCH success, can ceremonially burn all those revision notes about the classification of renal tubular acidosis until they come face to face on their next night shift with a child presenting with unexplained hypokalaemia. For those that enjoy the cerebral challenge, tubular physiology offers an insight into a fascinating organ; for those who want advice on investigating electrolyte abnormalities, we hope you will find practical guidance here.

In their entirety, renal tubular disorders are a heterogeneous group affecting different aspects of tubular function and as such may present in a variety of ways. This review will focus on those presenting primarily with electrolyte disorders but tubular disorders can also present with hypertension (e.g. Liddle syndrome or glucocorticoid suppressible hyperaldosteronism) or with renal calculi (hypercalciuria or cystinuria). Many of the tubular electrolyte disorders present with growth faltering and polyuria/polydipsia as a consequence of salt-wasting. The disorders are caused, directly or indirectly, through dysfunction of transporter proteins which are responsible for the tubular reabsorption or secretion of various electrolytes. Within the last two decades many genes encoding for these transporter proteins have been located and these genetic advances have served to improve our understanding of tubular physiology. However, as yet there is no gene therapy available for these challenging disorders.

This article will offer a flavour of tubular disorders by focussing on several of the more common tubulopathies. The individual conditions are illustrated through case presentations but the names of patients have been changed. Before the cases are presented, some understanding of renal homeostasis is needed.

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Renal physiology

The three major functions of the kidneys comprise:

- Homeostasis — the most important function of the kidneys. This is maintenance of a constant extracellular environment for optimum cell functioning.
- Hormone production including: erythropoietin for red blood cell production, andrenin, which converts angiotensinogen into angiotension I at the start of the renal-angiotensin system, in turn affecting renal and systemic haemodynamics.
- Other miscellaneous functions including hydroxylation of vitamin D (affecting calcium, phosphate and bone metabolism), peptide hormone catabolism and gluconeogenesis.

Homeostasis is achieved through the kidney excreting waste products (e.g. urea and uric acid) and specifically adjusting the urinary excretion of water and electrolytes (solute) to match the body's dietary intake and endogenous production through metabolism. Interplay with the renin-angiotensin system ensures homeostasis with regard to blood pressure control.

The human body contains around one million nephrons in each kidney. This is the functional unit of the kidney and its precise homeostatic function is achieved through differing properties of cells that define each segment of the tubule as well as a number of internal feedback mechanisms which require the close juxtaposition of the distal tubule with its parent glomerulus.

Each nephron comprises a glomerulus and tubule. The glomerulus, the initial part of the nephron, is a tuft of capillaries lined by epithelial cells. The endothelial cell and epithelial cell sandwich the glomerular basement membrane and these structures together constitute a sieve which results in a glomerular ultrafiltrate passing into Bowman's space at the start of the tubule. A schematic view of the nephron is shown in Figure 1.

The average adult glomerular filtration rate (GFR) is 125 ml/min per 1.73 m^2. Therefore the glomeruli of a healthy adult (whose average body surface area 1.73 m^2, hence the unusual units) filter 125 ml of plasma each minute or 180 litres each day. Since the average daily adult urine production is only 1.5 litres, over 99% of water is reabsorbed. That means the average 70 kg male with an extracellular fluid volume of 14 litres will turn it over around 13 times per day, hence homeostatic mechanisms with regard to electrolyte regulation need to be able to respond rapidly and precisely to avoid major perturbations in body chemistry.

In gross terms, the proximal tubule and loop of Henle are bulk resorbers of water and solute whilst the distal tubule has an important role in fine-tuning. The reabsorption may be across the tubular cells (transcellular) or passively across the tight junctions in between tubular cells (paracellular). It is the *polarity* of tubular cells that gives them their unique properties. Polarity means that the apical (that side of the cell adjacent to the tubular lumen) and basolateral (that side of the cell adjacent to peritubular capillaries)

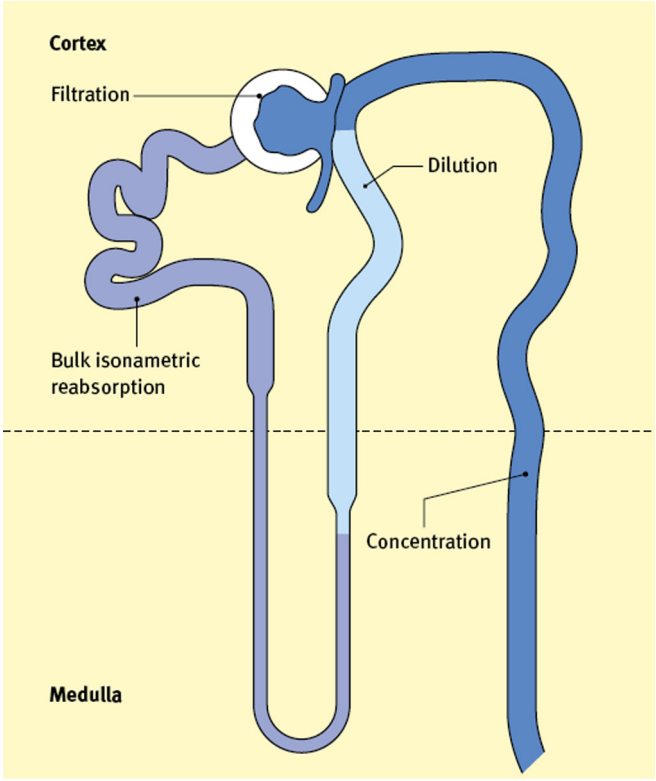

Figure 1 Simplified drawing of a nephron (from The renal system at a glance, O'Callaghan C, 2nd edition, chapter 1, p12, part of figure – note 4th edition now available). Publishers are Blackwell.

membranes have differing properties through expressing different channels or transporters. The polarity is maintained by the intercellular tight junctions. Most transport, both reabsorption and secretion, is linked directly or indirectly to sodium reabsorption. The sodium–potassium ATPase pump on the basolateral membrane actively pumps three sodium ions from the tubular cell into the peritubular space (where they are subsequently absorbed into peritubular capillaries) in exchange for two potassium ions, at the cost of one molecule of ATP. This active transporter thus generates a state of intracellular sodium depletion which favours entry of sodium from the tubular lumen down an electrochemical gradient. This is shown for bicarbonate absorption and hydrogen ion excretion in the proximal tubule in Figure 2.

Renal regulation of sodium balance

Sodium itself is reabsorbed through sodium channels or co-transporters which link the absorption of sodium to that of other molecules against their own electrochemical gradient. Around 65% of sodium is reabsorbed in the proximal tubule. The loop of Henle accounts for about 25% of sodium resorption. The (thin) descending limb is permeable to water but not sodium whereas the properties of thin ascending limb are the reverse. This allows the counter-current multiplier to work to create a hypertonic medullary insterstitium. This juxtaposition of the cortical collecting duct for the same nephron, where cells are permeable to water only under the influence of arginine vasopressin (anti-diuretic hormone) then uses this hypertonic medullary insterstitium to concentrate urine appropriately. In the thick ascending limb of the loop, the apical furosemide-sensitive

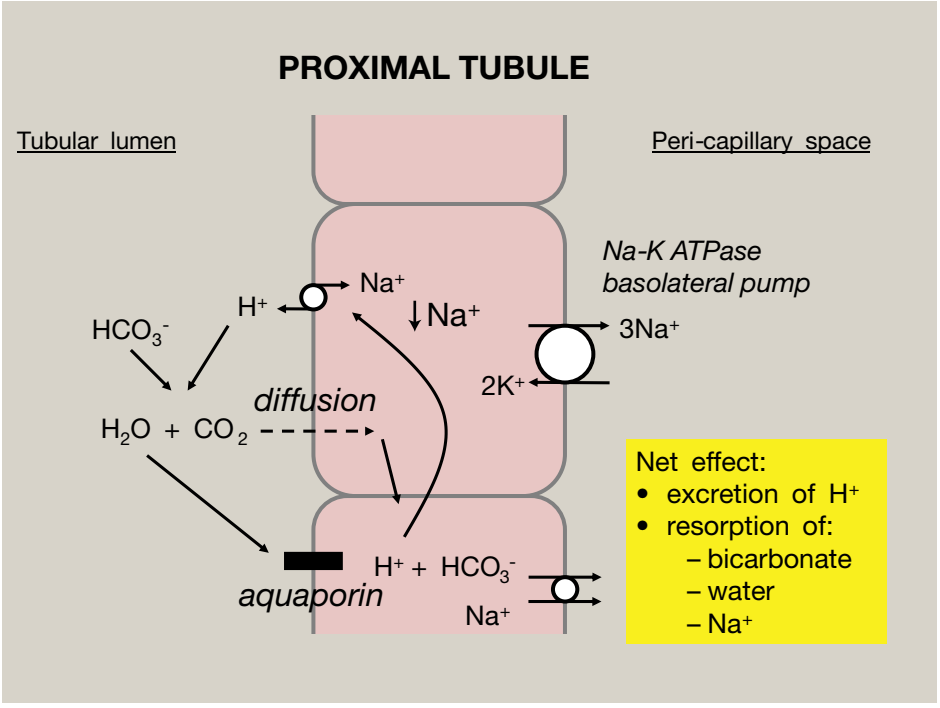

Figure 2 The driving force is the generation of a low intracellular sodium concentration which occurs due to the Na–K ATPase pump in the basolateral membrane pumping out three sodium ions in exchange for two potassium ions at the cost of one molecule of ATP.