The function of the nephron and the formation of urine

Stephen Kardasz

Learning objectives

After reading this article, you should be able to:

- name the segments of the nephron, and describe the physiological function of each segment
- describe how the nephron concentrates urine and name the hormones involved
- describe how common diuretics, such as furosemide, thiazides and spironolactone, exert an effect on urine concentration.

Abstract

The prime function of the kidney is to excrete nitrogenous waste products of metabolism while conserving nutrients and maintaining salt and water homeostasis. The basic functional unit of the kidney is the nephron. This article explains the purpose of each portion of the nephron and the transport systems and hormones involved in the normal function of the nephron in the formation of urine. The article includes a discussion of commonly used drugs that affect nephron function.

Keywords concentration; filtration; nephron; reabsorption; tubule

Introduction

The kidneys have many functions, including regulation of electrolyte balance, regulation of body fluids (osmolarity, volume and acid–base balance), conservation of useful substances (e.g. glucose, amino acids), production and secretion of hormones (endocrine gland) and gluconeogenesis. However, their prime function is to excrete waste products that either cannot be stored or are toxic. The main products that are excreted are nitrogen-containing molecules obtained from dietary sources because excess ingested nitrogen cannot be stored (unlike fats or carbohydrates). Mammals excrete these waste products in a solution – urine. As mammals evolved on dry land, water conservation is important. The mammalian kidney is, therefore, designed to excrete waste products, retain essential nutrients and keep water and salt loss to a bare minimum. All of these facts need to be appreciated to understand how and why the kidneys work.

The functional unit of the kidney is the nephron. Each adult kidney contains around 1–1.5 million nephrons. The basic structure of the nephron is shown in Figure 1. There are two types of nephron, the cortical and the juxtamedullary. The cortical nephron has a short loop of Henle, the tip of which dips into the outer medulla but does not enter the inner medulla. The juxtamedullary nephron has a very long loop of Henle that descends deeply into the medulla. The juxtamedullary nephrons create conditions in the medulla that allow the concentration of the urine later on in the nephron, should that be appropriate. The ratio of short- to long-loop nephrons varies between species: humans have about 15% juxtamedullary nephrons, whereas gerbils have about 50% juxtamedullary nephrons.

Each nephron comprises a glomerulus (tuft of capillaries and Bowman's capsule), which drains fluid into the tubular segment of the nephron. Each glomerulus is supplied by an afferent arteriole, which is a branch of the interlobular artery. The afferent arteriole divides into 2–5 branches that form capillary loops; these loops are known as the glomerular tuft. The tuft, in turn, is surrounded by a layer of epithelial cells known as Bowman's capsule. The blood vessels exit the glomerulus as the efferent arteriole (Figure 2).

The tubular segments of the nephron are an extension of Bowman's capsule. The first segment is the proximal tubule, which drains into the thin and thick segments of the loop of Henle, then into the distal tubule and collecting tubule, which finally drains urine into the renal pelvis.

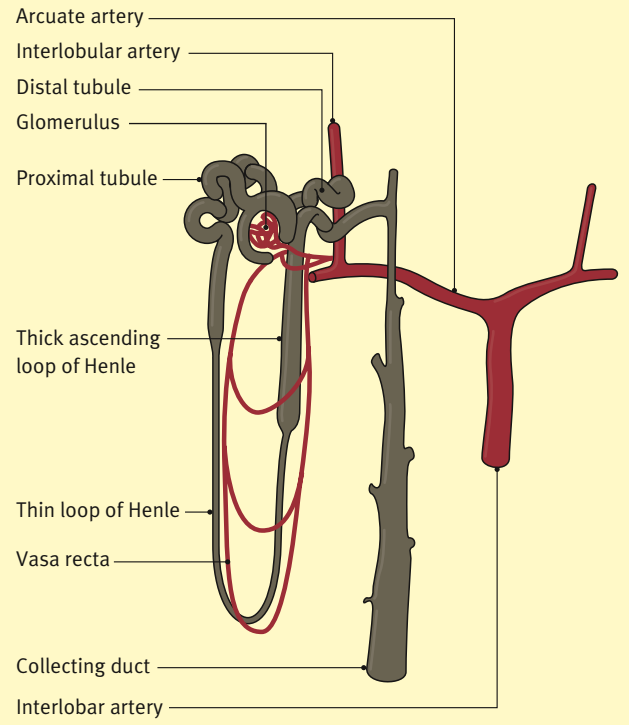

Figure 1

Stephen Kardasz *MB ChB FRCP (Lond) is a Consultant Nephrologist at the James Cook University Hospital, Middlesbrough, UK. He qualified from Manchester University in 1990, and trained in general medicine and nephrology in Manchester, Leicester and Glasgow, UK. He has special clinical interest in pre-dialysis care, renal failure in critical care and obstetric nephrology. Conflicts of interest: none declared.*

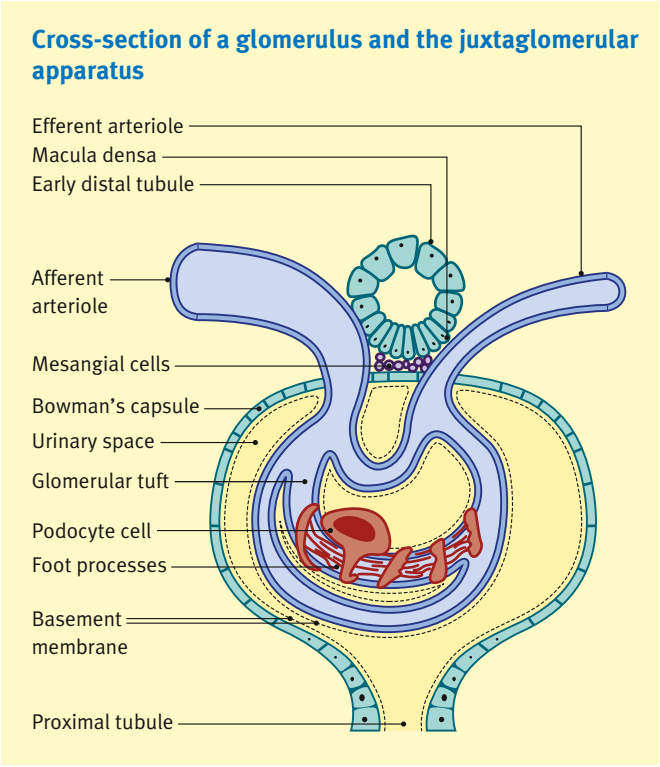

Figure 2

The glomerulus

The main function of the glomerulus is to form a filtrate from the circulating blood which is then modified by the tubule into urine. It is in essence a complex biological sieve. The plasma is filtered into the urinary space, which is the lumen of Bowman's capsule. Filtration is influenced by Starling forces and takes place because there is a differential resistance between the afferent and efferent arterioles. The efferent arteriole is relatively constricted compared with the afferent arteriole (this constriction is modulated by the action of angiotensin 2 and the sympathetic nervous system). Owing to this difference in resistance, the hydrostatic pressure within the glomerular tuft is increased, forcing a filtrate of plasma through the semipermeable vessels of the glomerular tuft.

The permeability of the tuft is highly selective because of its unique structure. The inner wall of the glomerular tuft is formed by thin endothelial cells which are covered by the basement membrane (BM). The BM is like a folded sac with an opening at the hilum, allowing the exit and entrance of the arterioles. The glomerular BM extends beyond the glomerulus and continues along the whole length of the nephron as the tubular BM. The BM is made up of a complex arrangement of collagen and proteoglycans. It is the proteoglycans that give the BM its negative charge, which is crucial for filtrate selectivity (see below).

The glomerular tuft comprises two other kinds of cells: mesangial cells and epithelial podocyte cells. The complex structure and function of the mesangium is poorly understood. It is known, however, that the mesangium contains microtubules, actin and myosin, which presumably forms the skeleton for the glomerular tuft.

The podocytes form the main filtration barrier. Despite the name, the structure of the podocyte can best be visualized as a hand rather than a foot. If one considers a small section of a capillary loop, the podocyte rests upon this as a hand gripping a tube. In this analogy, the palm of the hand is the body of the cell and contains the nucleus; the fingers form the foot processes. The fingers themselves are the primary processes, and branching at right angles from these are the interdigitating foot processes. The space between the foot processes, the slit diaphragm, is where filtration takes place. The surface of the foot processes and the slit diaphragm are covered in glycoproteins, which are also highly negatively charged.

The combined filtration barrier allows free passage of neutral substances of up to 4 nm in diameter; molecules larger than this are completely blocked (e.g. fibrinogen and immunoglobulins). Albumin has a diameter of about 3.6 nm and should, therefore, filter freely. The reason why virtually no albumin is filtered in the glomerulus is that albumin (as are most plasma proteins) is negatively charged and is therefore repelled by the negatively charged BM and slit diaphragm. To illustrate how efficient this system is, approximately 35,000 g of albumin passes through the kidneys in 24 hours (assuming a renal plasma flow of 600 ml/min and an albumin concentration of 40 g/l), yet, in normal subjects, less than 30 mg of albumin is excreted in the urine in 24 hours.

The proximal tubule

As explained above (and see Further Reading), healthy kidneys produce approximately 100–120 ml of filtrate per minute (the glomerular filtration rate; GFR). This equates to approximately 140–170 litres of filtrate being produced each day. Because an average adult produces only 2–3 litres of urine per day, it is clear that most of the function of the nephron and most of the energy used by the nephron relates to reabsorption of water and solutes.

The proximal tubule (PxT) is a highly metabolically active segment of the kidney, and accounts for reabsorption of approximately 65% of the filtered water and reabsorption of most solutes. The cells of the proximal tubule are, therefore, rich in mitochondria, have a large surface area as a result of microvilli on the apical surface and are freely permeable to water. The proximal tubule is divided into three segments (S1, S2 and S3), based on structural and functional differences. S1 is the initial short segment, S2 is the majority of the cortical segment and S3 is the straight medullary section; it is the S3 section that is most susceptible to ischaemic injury and acute tubular necrosis.

The PxT actively reabsorbs almost all the filtered glucose, amino acids, water-soluble vitamins and small proteins (e.g. β-microglobulin). It also reabsorbs the majority of the filtered sodium, potassium, chloride and bicarbonate. About 60% of filtered calcium and 80% of phosphate is also reabsorbed in the PxT. Most of these solutes are reabsorbed actively in the PxT. However, the reabsorption of other solutes in the PxT is limited; this is known as the tubular transport maximum (T*m*). The best known example of T*m* is that for glucose. In normal subjects, all glucose is rapidly reabsorbed in the PxT. However, in patients with poorly controlled diabetes mellitus, for example, the situation is different. Because the PxT has a finite capacity for reabsorption, once the concentration of glucose in the filtrate rises above approximately 11 mmol/l not all the filtered glucose is reabsorbed and some will pass through the PxT and can be detected in the urine (a small amount is reabsorbed in the distal