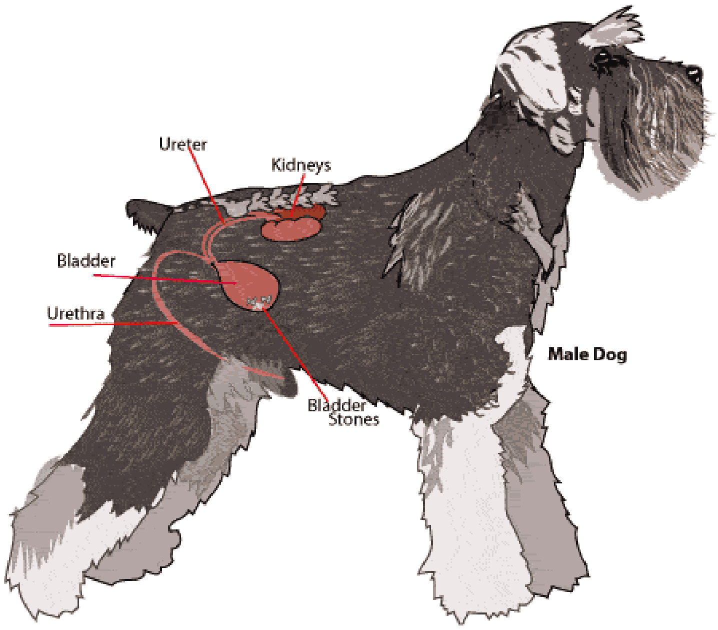
Structure and Function of the Kidney 1

Veterinary Bioscience: Metabolism and Excretion



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Learning objectives

1. Define the main functions of the kidneys
2. Describe the functional anatomy of the nephron
3. Discuss the importance of renal haemo-dynamics to kidney function
4. Explain how glomerular filtration occurs, why it is important and the factors which regulate it
5. Explain the tubular processes involved in producing and modifying urine

I. BASIC CONCEPTS OF RENAL PHYSIOLOGY

Functions of the kidney

The kidneys have a number of important functions

1. Function as a filter to excrete water and soluble metabolic waste products from the body. These include non-volatile end products of metabolism such as urea, ammonium, uric acid, creatinine, bilirubin, foreign drugs and toxins.
2. Maintain a stable internal environment by regulating electrolytes, (Na^{+}, K^{+}, Cl^{-} $Ca^{2+}Mg^{2+}$, $PO_4{}^{2-}$) and H+ (pH).
3. Regulating body fluid osmolality and volume status through changes primarily in water and sodium content.
4. Kidneys produce or activate a number of hormones
   a. Renin which is involved in the regulation of sodium, blood volume, blood pressure and blood flow.
   b. 1,25-dihydroxycholecalciferol (calcitriol), which is derived from vitamin D3 (active vitamin D). This hormone enhances intestinal absorption of calcium.
   c. Erythropoietin, which regulates RBC production by the bone marrow.
   d. Prostaglandin that can control blood vessel tone.

Functional anatomy of the kidney.

The urinary system consists of two kidneys and the urine produced by each kidney drains through a separate ureter to the bladder. Form the bladder the urethra transports the urine outside the body. Kidneys have a combined weight less than 0.5-1.0% of body weight .

They have an outer cortex containing the renal corpuscle (bowman's capsule and glomerulus), the proximal and distal convoluted tubules of the nephron and the peritubular capillaries. Below the cortex is an inner layer the medulla which contains the, loop of Henle, the collecting duct and vasa recta

Blood enters the kidneys through the renal artery that divides into serial branches (interlobar, arcuate and interlobular arteries and afferent arteriole) before entering the glomerulus to become glomerular capillaries. Blood leaves the glomerulus via the efferent arterioles which leads to peritubular capillaries (that surround the tubule) or vasa recta capillaries that coalesce into veins (interlobular, arcuate and interlobar) before forming the renal vein. Large volumes of blood (~20% of cardiac output) is delivered to the kidneys.

Nephron

The nephron is made up of the renal corpuscle (glomerulus and Bowmans capsule) and the tubule. There are different numbers of nephrons in different species. For example cats have 190,000 nephrons and dogs 400,000 nephrons. Nephrons can be subdivided into superficial nephrons in outer cortex and juxtamedullary nephrons near the corticomedullary junction. Cortical nephrons have short loops of Henle in the outer medulla whereas juxtamedullary nephrons and have long loops of Henle that travel deep into the inner medulla.

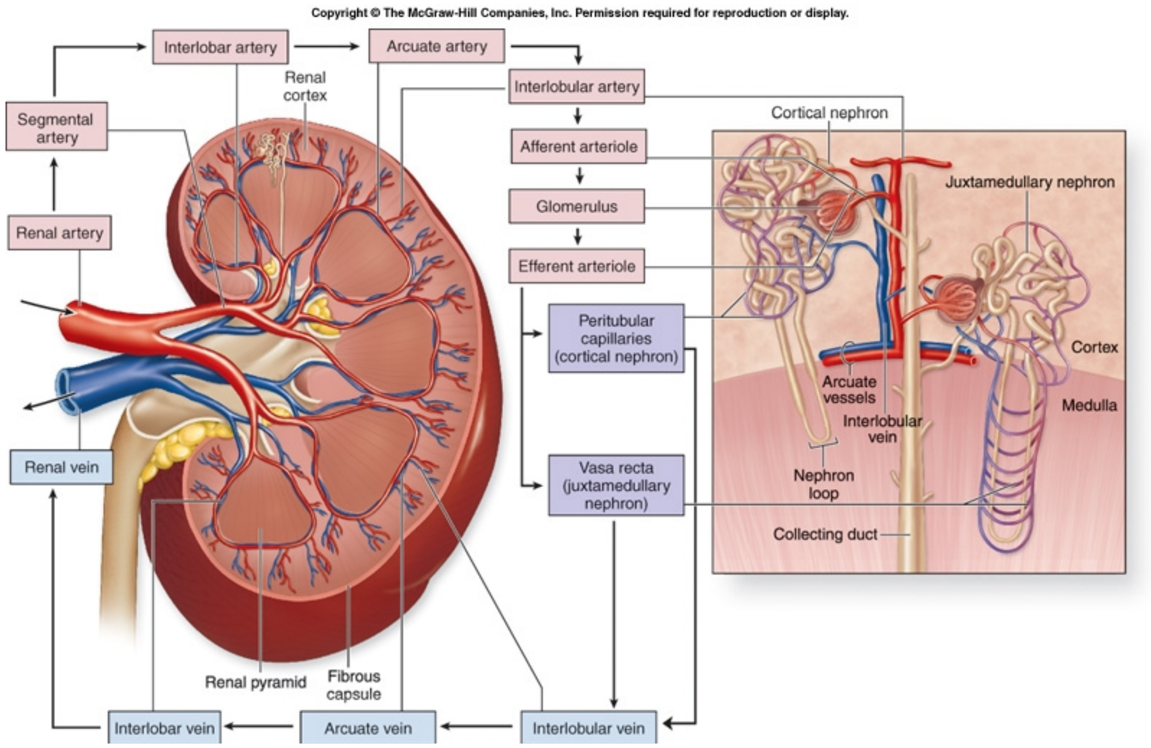

Fig 1 Structure of the kidney. Sherwood Human physiology. 2012.

Renal Corpuscle

The renal corpuscle consists of the glomerulus and the Bowman's capsule. Glomerulus is a cluster of capillaries surrounded by the Bowman's capsule made up of an outer parietal layer of simple squamous epithelium and inner visceral layer made up of podocytes which lie below the basement membrane of the capillaries. Blood is filtered out of the capillaries into Bowmans space which is situated between the two layers. Glomerulus also contains mesangial (modified smooth muscle contractile cells) that support the capillary loops. High hydrostatic pressure within the glomerulus force water, ions and small molecules through the filtration barrier (endothelial pores, basement membrane and filtration slits) into the Bowman's space. Large proteins and cellular elements are unable to be filtered. The urinary filtrate in the Bowmans space drains to the tubule which contains anatomically and functionally distinct segments that modify the volume and content of the tubular fluid by the processes of tubular reabsorption or secretion.

Tubular function

Proximal tubule

The proximal tubule is composed of both convoluted and straight regions lined by columnar epithelial cells. Most reabsorption of filtered solutes and water takes place here. The epithelial cells of the convoluted proximal tubule have a prominent microvilli covered brush border that gives it a large surface area that facilitates the reabsorption of large quantities of filtered water and solutes.

Loop of Henle

Loop of Henle is involved in concentrating urine. It does this by generating a vertical hypertonic medullary gradient through a process known as counter current exchange.

Juxtaglomerular apparatus

The Juxtaglomerular apparatus is a combination of the macula densa a plaque like structure in the wall of the distal tubule where it passes between afferent and efferent arterioles and juxtaglomerular cells (also termed granular cells) located within wall of the afferent arteriole.

The juxtaglomerular apparatus has an important role in tubuloglomerular feedback mechanism which controls blood flow in the glomerulus and in the secretion of renin from juxtaglomerular cells which is important in regulating Na+ reabsorption and blood pressure

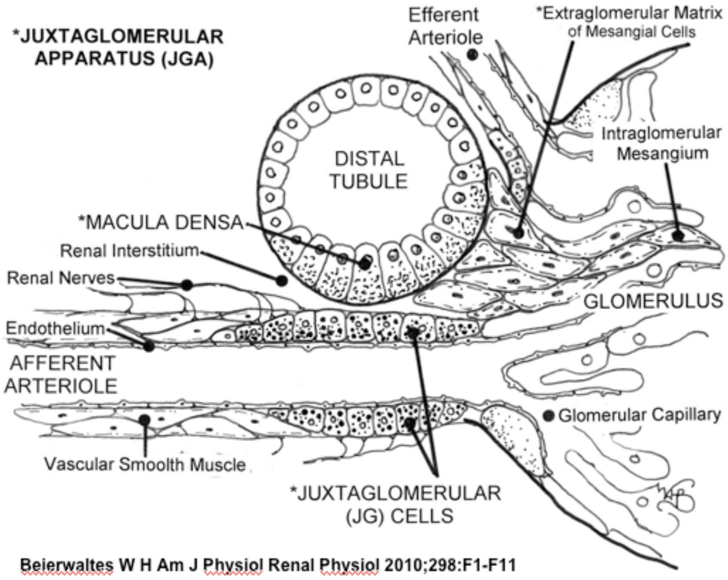

Fig 2 Structure of juxtaglomerular apparatus

Distal nephron

The distal nephron is present after the macula densa at the end of the cortical thick ascending limb. It consists of the distal tubule, the connecting segment and cortical and medullary collecting ducts which can be separated by both histological appearance and hormone responsiveness. The collecting ducts contain two characteristic cell types (principal and intercalated cells). In the distal tubule urine is maximally concentrated, potassium is secreted, acidification occurs and it is the final site of sodium reabsorption.
Key hormones that act on the distal nephron are calcitriol and parathyroid hormone (distal tubule and connecting tubule), aldosterone (connecting tubule and collecting ducts) and antidiuretic hormone (collecting tubules).

Blood vessels associated with the loop of Henle

The vasa recta is a long hair-pin shaped capillary network that follow the loop of Henle deep into the medulla. It supplies nutrients to the tubule and are highly permeable to solute and water.

Nerves

Nephron is innervated with sympathetic nerves ending at the afferent & efferent arterioles (important in regulating blood flow through the glomerulus) through vasoconstriction, juxtaglomerular cells (renin release) and tubular epithelial cells (promotes Na+ reabsorption via altering transepithelial transport mechanisms across the tubule cells).

2. BASIC RENAL PROCESSES

Renal function consists of three basic processes:

1. Glomerular filtration: filtration of blood. The glomerular filtrate contains solute concentrations similar to those in plasma but excludes medium to high molecular weight proteins and formed cellular components.
2. Tubular reabsorption: movement of fluid and solutes from tubular lumen to peritubular capillary. Fluid and solutes filtered at the glomerulus are largely recovered by tubular reabsorption.

3. Tubular secretion: movement of solutes from the peritubular capillary to the tubular lumen.

Glomerular Filtration

1. Glomerular filtration is the first step in forming urine. Blood is filtered by a pressure gradient from the glomerular capillaries through a filtration barrier into the Bowman's space.

2. Glomerular filtration rate (GFR) = Volume per unit time at which ultrafiltrate is produced by the glomerulus. In adult dogs 3.39-4.6 ml/min/kg ~(115L/day for a 20kg dog).

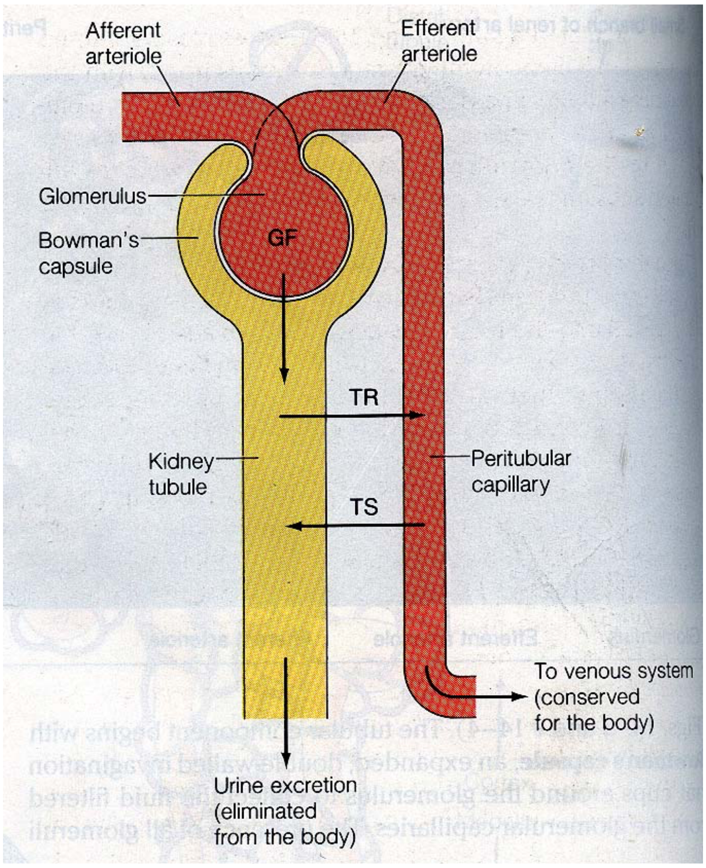

Fig 4 . Basic renal processes, Sherwood 2007

Glomerular filter barrier comprises 4 layers

1. A glycocalyx on endothelial cells: this covers the luminal surface of endothelial cells and consists predominately of negatively charged glycosaminoglycans.
2. Endothelial cells: Fenestrated endothelium with numerous 50-100nm pores. Limit filtration of cellular elements
3. Glomerular basement membrane: Contains negatively charged glycoproteins and mucopolysaccharides. It has multiple layers made up of heparan sulfate proteoglycans , type IV collagen laminin and podocalyxin.
4. Epithelial podocytes: Podocytes are modified epithelial cells and are part of the visceral layer of the Bowman' capsule. They have numerous interdigitating footlike processes that cover the basement membrane. Between the footlike processes a protein network consisting of nephrin, neph1 and podocin forms filtration slits that have pores of 1.8-4.4nm.

Properties of glomerular filtrate

Molecular size and charge dictates whether a substance is filtered. Glomerular filtrate is “essentially” protein free whereas water and small solutes are freely filtered. Progressive increase in molecular sieving with size. Molecules r <1.8 nm (~MW 10,000 Da) freely filtered. r > 4.4 nm (~MW 80,000 Da) not filtered. Some low molecular weight substances are bound to protein and are therefore poorly filtered eg drugs such as penicillin, aspirin, atropine and morphine.

Nature of the glomerular barrier to macromolecules

1. Steric –, basement membrane & slits;
2. Electrostatic - extracellular matrix consists mainly of polyanions; thus, negatively charged macromolecules are restricted. Large numbers of plasma proteins are negatively charged, so they are hindered electrostatically.

Glomerular filtration is a bulk-flow process. The hydrostatic pressure difference across the capillary wall generated from a combination of systemic blood pressure and afferent and efferent arteriole vascular tone favours filtration, while the protein concentration difference across the capillary wall creates an osmotic force that opposes filtration.

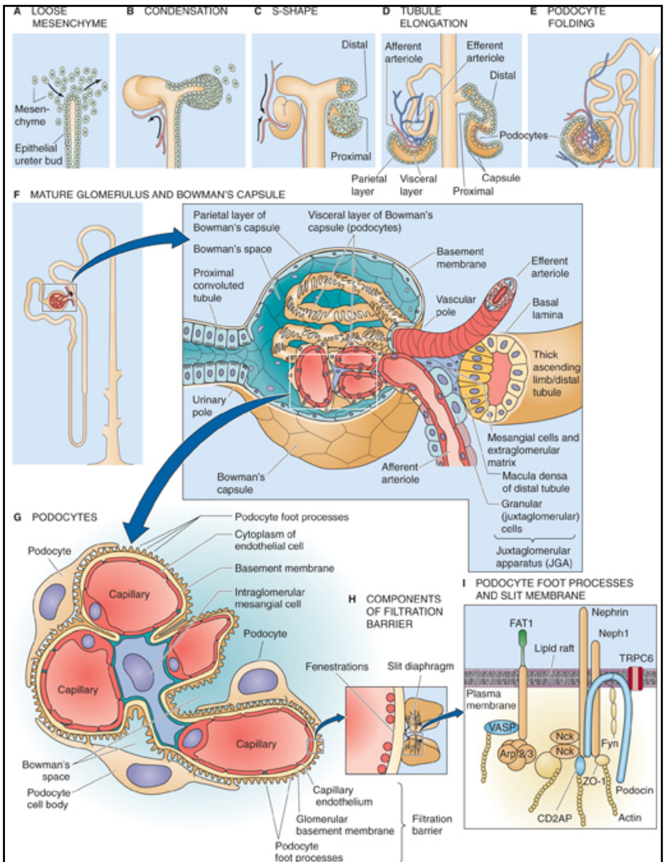

Fig.5 Filtration barrier within the glomerulus

Forces involved in filtration and net filtration pressure

Net filtration pressure (NFP) is the sum of the opposing hydrostatic and colloid osmotic (oncotic) pressures acting across the capillary.

$NFP = (PGC + \pi BC) - (PBC + \pi GC)$

PGC = hydrostatic pressure in the glomerular capillary

πBC = oncotic pressure of fluid in Bowman's space

PBC = hydrostatic pressure in Bowman's space

πGC= oncotic pressure in the glomerular capillary

Normally, there is no protein in Bowman's space, so $\pi BC = 0$.
Therefore, NFP = PGC - PBC - πGC
In dogs: NFP= = 60 mmHg – 15mmHg - 27mmH = 18mmHg thus driving filtration.

GFR = Kf x NFP.

- Kf =filtration coefficient (product of the hydrostatic permeability and the glomerular surface area).
- GFR can be altered by changing Kf or any of the Starling forces. Hydrostatic pressure is reduced by afferent arteriolar constriction and increased by efferent arteriolar constriction.
- Glomerular capillaries are very permeable and have a large surface area available for filtration. Mesangial cells (smooth muscle type cells) are present in the glomerulus between capillary loops) and have contractile activity. They act to restrict blood flow through capillaries thereby dropping GFR when they contract.
- Podocytes can also be relaxed to increase slit size.

Renal blood
Blood flow is 20% cardiac output.
Filtration fraction (FF) represents the proportion of the fluid reaching the kidneys that is filtered into the tubules. FF= GFR/RPF (renal plasma flow) = 20%
ie ~ 20% of blood is filtered remainder goes into efferent arteriole and peritubular capillary.

Whilst GFR is the main determinant of renal function if blood flow is reduced eg renal artery stenosis then blood flow and GFR is reduced. Kidneys regulate their blood flow and GFR by adjusting vascular resistance. Otherwise urinary excretion of solute and water would alter with changes in arterial blood pressure

GFR Determinants	Major factors that tend to increase the magnitude of the direct determinant
K_f	Decreased glomerular surface area due to contraction of glomerular mesangial cells **Result: decreased GFR**
P_{GC}	Increased renal arterial pressure or Decreased afferent arteriolar resistance (dilation) or Increased efferent arteriolar resistance (constriction) or **Result Increased GFR**
P_{BC}	Increased intratubular pressure due to obstruction of renal tubule or extrarenal urinary system **Result: Decreased GFR**
π_{GC}	Increased systemic plasma oncotic pressure Decreased total renal plasma flow **Result: Decreased GFR**

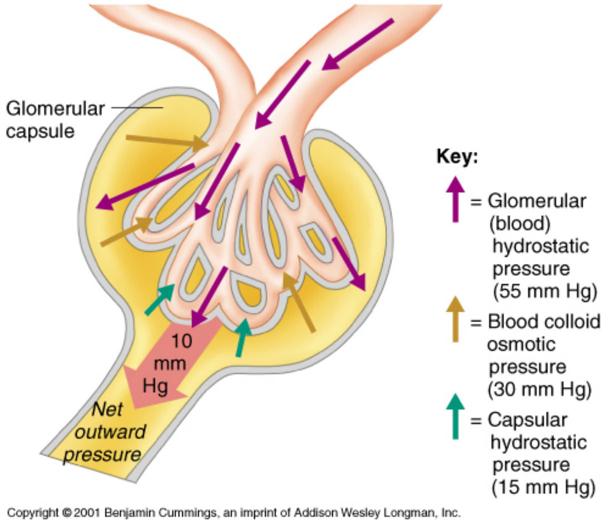

Fig 6 Starling forces within the glomerulus

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