

PHYSIOLOGY OF THE KIDNEY

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The Functions of the Kidney

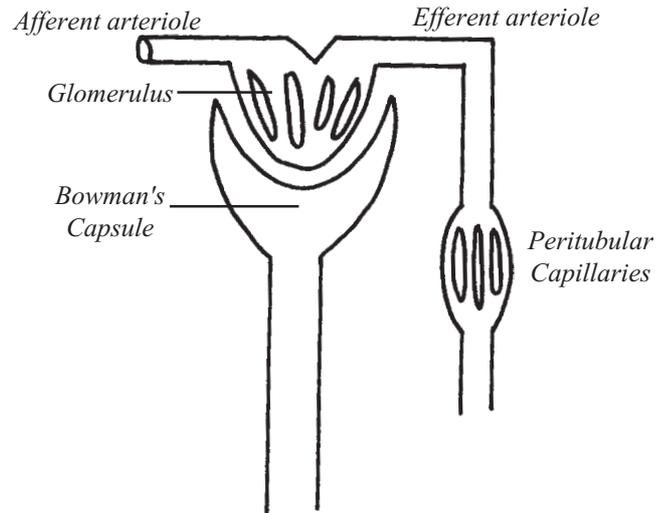
- Regulation of the water and electrolyte content of the body.
- Retention of substances vital to the body such as protein and glucose
- Maintenance of acid/base balance.
- Excretion of waste products, water soluble toxic substances and drugs.
- Endocrine functions.

Regulation of the water and electrolyte content of the body

The kidney allows a person to eat and drink according to their habits without changing the composition of their fluid compartments.

Renal Blood Supply is normally is about 20% of the cardiac output. Approximately 99% of the blood flow goes to the cortex and 1% to the medulla. The cortex is the outer part of the kidney containing most of the nephrons. The medulla is the inner part of the kidney and contains the specialised nephrons in the juxta-medullary region, immediately next to

the medulla. These nephrons have a greater concentrating ability, the mechanism being explained below. The kidney is unique as it has two capillary beds arranged in series, the glomerular capillaries which are under high pressure for filtering, and the peritubular capillaries which are situated around the tubule and are at low pressure (figure 1). This permits large volumes of fluid to be filtered and reabsorbed.



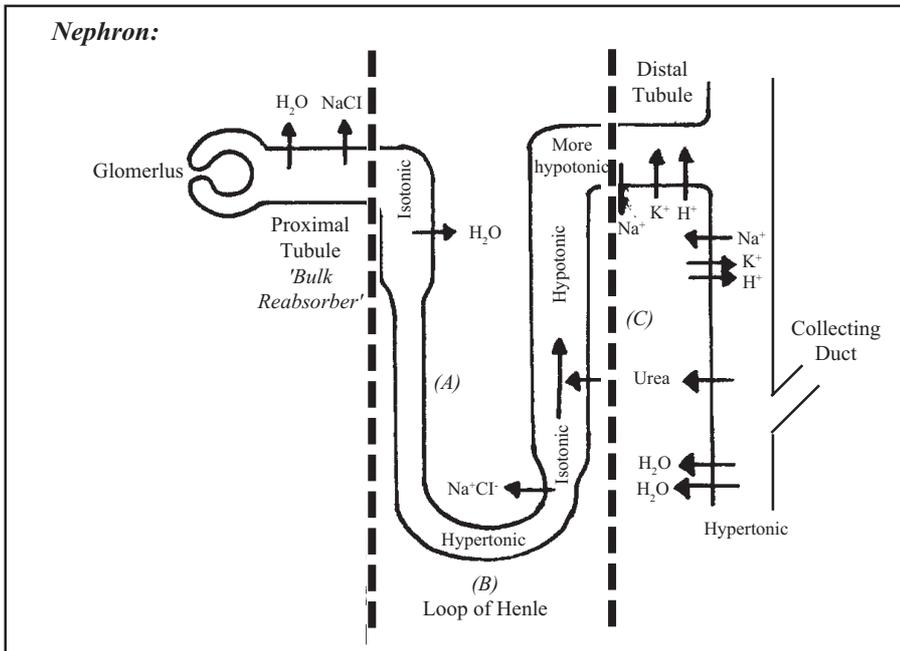
The Nephron: Each kidney consists of about one million nephrons. The nephron is made up of a glomerulus and its tubule (figure2). The tubule is

made up of a number of sections, the proximal tubule, the medullary loop (loop of Henle), and the distal tubule which finally empties into the collecting duct.

autoregulation of renal blood flow and a feedback mechanism known as “glomerular tubular balance”.

Glomerular Tubular balance. When there is a decrease in GFR, there is a resulting decrease in the

fluid flow rate within the tubule. At the loop of Henle, there is greater time for reabsorption of sodium and chloride ions. Therefore there is a decrease in the number of sodium and chloride ions reaching the distal tubule which is detected by the macula densa. This in turn decreases the resistance in the afferent arteriole which results in an increase in renal blood flow. It also increases renin release from the juxtaglomerular apparatus which stimulates angiotensin II production causing constriction of the



effluent arteriole.

Urine is formed as a result of a three phase process - **simple filtration, selective and passive reabsorption and excretion.**

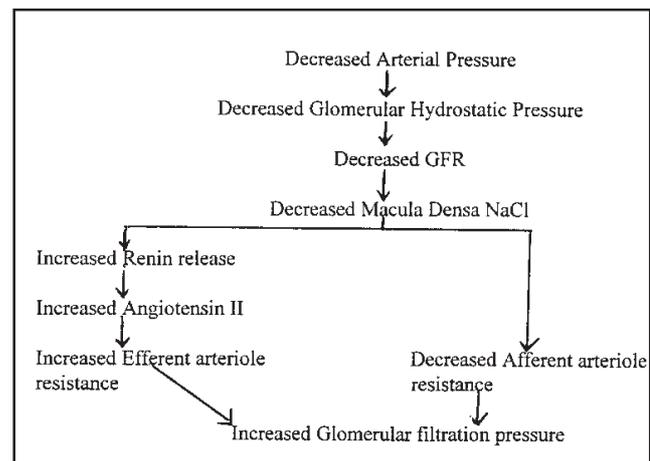
Filtration

Filtration takes place through the semipermeable walls of the glomerular capillaries which are almost impermeable to proteins and large molecules. The filtrate is thus virtually free of protein and has no cellular elements. The glomerular filtrate is formed by squeezing fluid through the glomerular capillary bed. The driving hydrostatic pressure (head of pressure) is controlled by the afferent and efferent arterioles, and provided by arterial pressure. About 20% of renal plasma flow is filtered each minute (125 ml.min⁻¹). This is the **glomerular filtration rate (GFR).**

These both act to increase the hydrostatic pressure in the glomerular capillary bed and return GFR to normal (table 1).

The **juxtaglomerular complex** consists of **macula densa cells**, which are special distal tubular epithelial cells which detect chloride concentration and modified smooth muscle cells, **juxtaglomerular cells**, in the walls of the afferent and efferent arteriole. These cells produce renin. **Renin** is an enzyme which converts the plasma protein angiotensinogen to **angiotensin I**. Angiotensin converting enzyme (ACE) which is formed in small

Table 1



In order to keep the renal blood flow and GFR relatively constant hydrostatic pressure in the glomerulus has to be kept fairly constant. When there is a change in arterial blood pressure, there is constriction or dilatation of the *afferent* and *efferent* arterioles, the muscular walled vessels leading to and from each glomerulus. This process is called **autoregulation.**

Autoregulation of GFR is achieved by

quantities in the lungs, proximal tubule and other tissues, converts **angiotensin I** to **angiotensin II** which causes vasoconstriction and an increase in blood pressure. Angiotensin II also stimulates the adrenal gland to produce **aldosterone** which causes water and sodium retention which together increase blood volume.

This is a negative feedback system. In other words the initial stimulus is a fall in blood volume which leads to a fall in perfusion pressure in the kidneys. When blood volume, renal perfusion and GFR improve the system feeds back to switch off or turn down the response to the stimulus.

Selective and Passive Reabsorption

The function of the **renal tubule** is to reabsorb selectively about 99% of the glomerular filtrate.

The **Proximal Tubule** reabsorbs 60% of all solute, which includes 100% of glucose and amino acids, 90% of bicarbonate and 80-90% of inorganic phosphate and water.

Reabsorption is by either active or passive transport. Active transport requires energy to move solute against an electrochemical or a concentration gradient. It is the main determinant of oxygen consumption by the kidney. Passive transport is where reabsorption occurs down an electrochemical, pressure or concentration gradient.

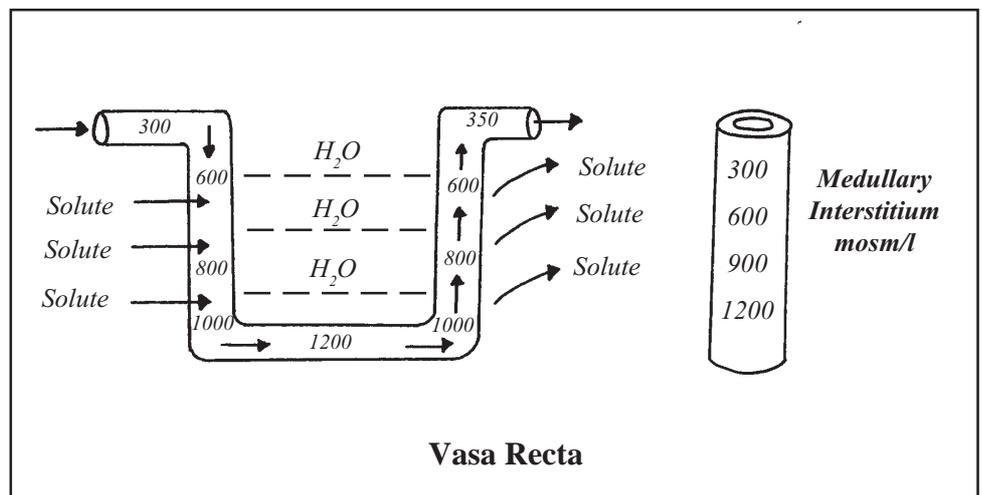
Most of the solute reabsorption is active, with water being freely permeable and therefore moving by osmosis. When the active reabsorption of solute from the tubule occurs, there is a fall in concentration and hence osmotic activity within the tubule. Water then moves because of osmotic forces to the area outside the tubule where the concentration of solutes is higher.

The **Loop of Henle** is the part of the tubule which dips or “loops” from the cortex into the medulla, (**descending limb**), and then returns to the cortex, (**ascending limb**). It is this part of the tubule where urine is concentrated if necessary. This is possible because of the high concentration of solute in

the substance or interstitium of the medulla. This high concentration of solutes is maintained by the **counter current multiplier**. A counter current multiplier system is an arrangement by which the high medullary interstitial concentration of solute is maintained, giving the kidney the ability to concentrate urine. The loop of Henle is the counter current multiplier and the **vasa recta** is the counter current exchanger, the mechanism being described below.

Actions of different parts of the loop of Henle

- A** The **descending loop of Henle** is relatively impermeable to solute but permeable to water so that water moves out by osmosis, and the fluid in the tubule becomes hypertonic.
- B** The thin section of the ascending loop of Henle is virtually impermeable to water, but permeable to solute especially sodium and chloride ions. Thus sodium and chloride ions move out down the concentration gradient, the fluid within the tubule becomes firstly isotonic then hypotonic as more ions leave. Urea which was absorbed into the medullary interstitium from the collecting duct, diffuses into the ascending limb. This keeps the urea within the interstitium of the medulla where it also has a role in concentrating urine.
- C** The thick section of the ascending loop of Henle and early distal tubule are virtually impermeable to water. However sodium and chloride ions are actively transported out of the tubule, making the tubular fluid very hypotonic.



The **Vasa Recta** (figure 3) is a portion of the peritubular capillary system which enters the medulla where the solute concentration in the interstitium is high. It acts with the loop of Henle to concentrate the urine by a complex mechanism of counter current exchange. If the vasa recta did not exist, the high concentration of solutes in the medullary interstitium would be washed out. Solutes diffuse out of the vessels conducting blood towards the cortex and into the vessels descending into the medulla while water does the opposite, moving from the descending vessels to the ascending vessels. This system allows solutes to recirculate in the medulla and water, in effect, to bypass it.

Distal Tubule and Collecting Duct: The final concentration of urine depends upon the amount of **antidiuretic hormone (ADH)** secreted by the posterior lobe of the pituitary. If ADH is present the distal tubule and the collecting duct become permeable to water. As the collecting duct passes through the medulla with a high solute concentration in the interstitium, the water moves out of the lumen of the duct and concentrated urine is formed. In the absence of ADH the tubule is minimally permeable to water so large quantities of dilute urine is formed.

There is a close link between the hypothalamus of the brain and the posterior pituitary. There are cells within the hypothalamus, **osmoreceptors**, which are sensitive to changes in osmotic pressure of the blood. If there is low water intake, there is a rise in osmotic pressure of the blood, and after excess intake of water, the reverse. Nerve impulses from the hypothalamus stimulate the posterior pituitary to produce ADH when the osmotic pressure of the blood rises. As a result water loss in the kidney is reduced because ADH is secreted, and water reabsorbed in the collecting duct.

Acid/Base Function

- **Acid:** a substance that can release hydrogen ions in solution.
- **Base:** a substance that can accept hydrogen ions in solution.
- **Buffer:** a substance whose pKa (the pH at which half is in the ionised form and half unionised) is close to the pH of its environment. In those circumstances, addition

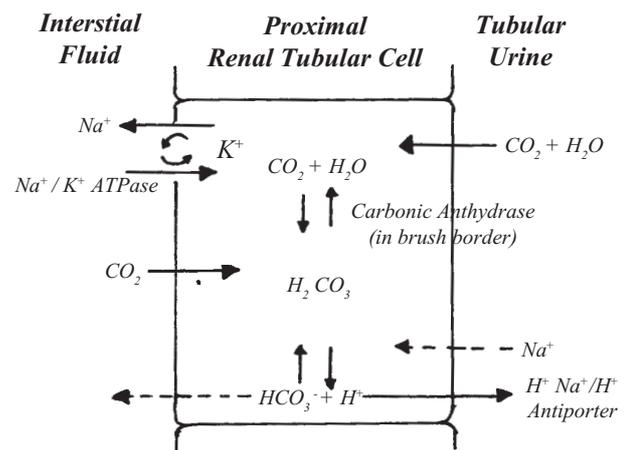
or removal of hydrogen ions results in minimal change to pH, the purpose of the buffer.

- The pH is the negative log to base 10 of the hydrogen ion concentration $[H^+]$ and indicates the acidity of the solution. The more acid the solution the **higher** the H^+ concentration but the **lower** the pH. The pH in the body is kept under tight control as almost all enzyme activities in the body are dependent on the pH being normal.

The lungs and kidneys work together to produce a normal extracellular fluid and arterial pH of 7.35-7.45 (34-46 $nmol.l^{-1}$ H^+ concentration). Carbon dioxide (CO_2), when dissolved in the blood is an acid, and is excreted by the lungs. The kidney excretes fixed acid and performs three functions to achieve this:-

1. **Tubular secretion of acid** (figure 4): The buffer sodium bicarbonate, is filtered by the glomerulus and then reabsorbed in the proximal tubule. The sodium is absorbed by a sodium/hydrogen ion pump (Na^+/H^+) exchanging Na^+ for H^+ on the luminal proximal border of the tubular cell. A sodium/potassium pump (Na^+/K^+) forces Na^+ through the cell from tubular fluid in exchange for potassium.

Bicarbonate Reabsorption:



2. **Glomerular filtration of buffers** which combine with H^+ :
 - a) The majority of the filtered bicarbonate is reabsorbed (90% in the proximal tubule). The H^+ , released as the Tubular Secretion of Acid (above), forms carbonic acid with the bicarbonate (HCO_3^-). $H^+ + HCO_3^- \rightleftharpoons H_2CO_3$

Carbonic anhydrase, found in the proximal tubular cells, catalyses the reaction to carbon dioxide (CO_2) and water (H_2O) (figure 4). The CO_2 diffuses into the cell where it again forms carbonic acid in the presence of carbonic anhydrase. The carbonic acid ionises to H^+ and HCO_3^- . The H^+ is then pumped out of the cell back to the lumen of the tubule by the Na^+/H^+ pump (1 above) and the sodium is returned to the plasma by the Na^+/K^+ pump (1 above). Water is absorbed passively.

- b) Other buffers include inorganic phosphate (HPO_4^-), urate and creatinine ions which are excreted in urine as acid when combined with H^+ ions secreted in the distal nephron
3. **Ammonia is produced** enzymatically from glutamine and other amino acids, and is secreted in the tubules. Ammonia (NH_3) combines with secreted H^+ ions to form a non-diffusible ammonium ion (NH_4^+) which is excreted in the urine. Ammonia production is increased by a severe metabolic acidosis to as much as $700 \text{ mmol}\cdot\text{day}^{-1}$.

Excretion of waste products

Filtration occurs as blood flows through the glomerulus. Some substances not required by the body, and some foreign materials (e.g. drugs) may not be cleared by filtration through the glomerulus. Such substances are cleared by *secretion* into the tubule and excreted from the body in the urine.

Hormones and the Kidney

Renin (see above) increases the production of angiotensin II which is released when there is a fall in intravascular volume e.g. haemorrhage and dehydration. This leads to:

- Constriction of the efferent arteriole to maintain GFR, by increasing the filtration pressure in the glomerulus.
- Release of aldosterone from the adrenal cortex
- Increased release of ADH from the posterior pituitary
- Thirst
- Inotropic myocardial stimulation and systemic arterial constriction

The opposite occurs when fluid overload occurs.

Aldosterone promotes sodium ion and water reabsorption in the distal tubule and collecting duct where Na^+ is exchanged for potassium (K^+) and hydrogen ions by a specific cellular pump. Aldosterone is also released when there is a decrease in serum sodium ion concentration. This can occur, for example, when there are large losses of gastric juice. Gastric juice contains significant concentrations of sodium, chloride, hydrogen and potassium ions. Therefore it is impossible to correct the resulting alkalosis and hypokalaemia without first replacing the sodium ions using 0.9% saline solutions.

Atrial Natriuretic Peptide (ANP) is released when atrial pressure is increased e.g. in heart failure or fluid overload. It promotes loss of sodium and chloride ions and water chiefly by increasing GFR.

Antidiuretic Hormone (ADH) increases the water permeability of the distal tubule and collecting duct, thus increasing the concentration of urine. In contrast, when secretion of ADH is inhibited, it allows dilute urine to be formed. This occurs mainly when plasma sodium concentration falls such as following drinking large quantities of water. This fall is detected by the osmoreceptors (above). The hormones interact when blood loss or dehydration occurs to maintain intravascular volume. The flow diagram in Table 2 illustrates this.

Other Substances Produced by the kidney

1,25 dihydroxy vitamin D (the most active form vitamin D) which promotes calcium absorption from the gut.

Erythropoietin which stimulates red cell production

Both of these decrease in renal failure.

Table 2. The Kidney and maintenance of Intravascular volume

