ZOOACOR09T- PHYSIOLOGY

UNIT 6 RENAL PHYSIOLOGY

MECHANISM OF URINE FORMATION

REGULATION OF ACID-BASE BALANCE

Overview

MECHANISM OF URINE FORMATION

Urine formation begins with the delivery of blood to the glomerulus followed by its filtration past the glomerular barrier. The filtered portion of plasma continues through the nephron whereas the unfiltered portion passes into the peritubular capillaries. As the filtered portion travels through the nephron, water and certain solutes are resorbed back into the peritubular capillaries whilst other solutes are secreted from the peritubular capillaries into the nephron. Whatever fluid is remains at the end of the nephron is discarded as urine.

Urine formation in our body is mainly carried out in three phases namely

1. Glomerular filtration or Ultrafiltration,
2. Tubular Reabsorption
3. Tubular Secretion.

Glomerular filtration

Glomerulus filters out substances of low molecular weight from the blood with the retention of substances of high molecular weight, especially the proteins. Therefore, proteins are retained in the glomeruli and are not normally found in urine. If protein is detected in the urine, it indicates the kidney damage or other disease which affect the glomerular membrane.

Thus water and many dissolved substances from the blood are filtered into the lumen of the Bowman's capsule through its walls. The glomerular filtrate contains a large amount of water and other dissolved substances such as urea, uric acid, creatinine, amino-acids, glucose, sodium, potassium, vitamins, etc. The blood flows into efferent renal arterioles. Thus the glomerular filtrate and blood plasma are similar except that glomerular filtrate does not have proteins and fats.

In normal adult, two million nephrons filter one litre of blood each minute to give about 1200 ml of glomerular filtrate (primary urine) at Bowman's Capsule. Therefore, the Glomerular Filtration Rate (GFR) in adult is about 120 ml per minute. The hydrostatic pressure of the blood in the glomerular capillaires (P_g) is the main force for driving the fluid (Water and solute) out of the glomerulus.

Therefore, the effective filtration pressure (P_{ef}) is calculated by the following relation:

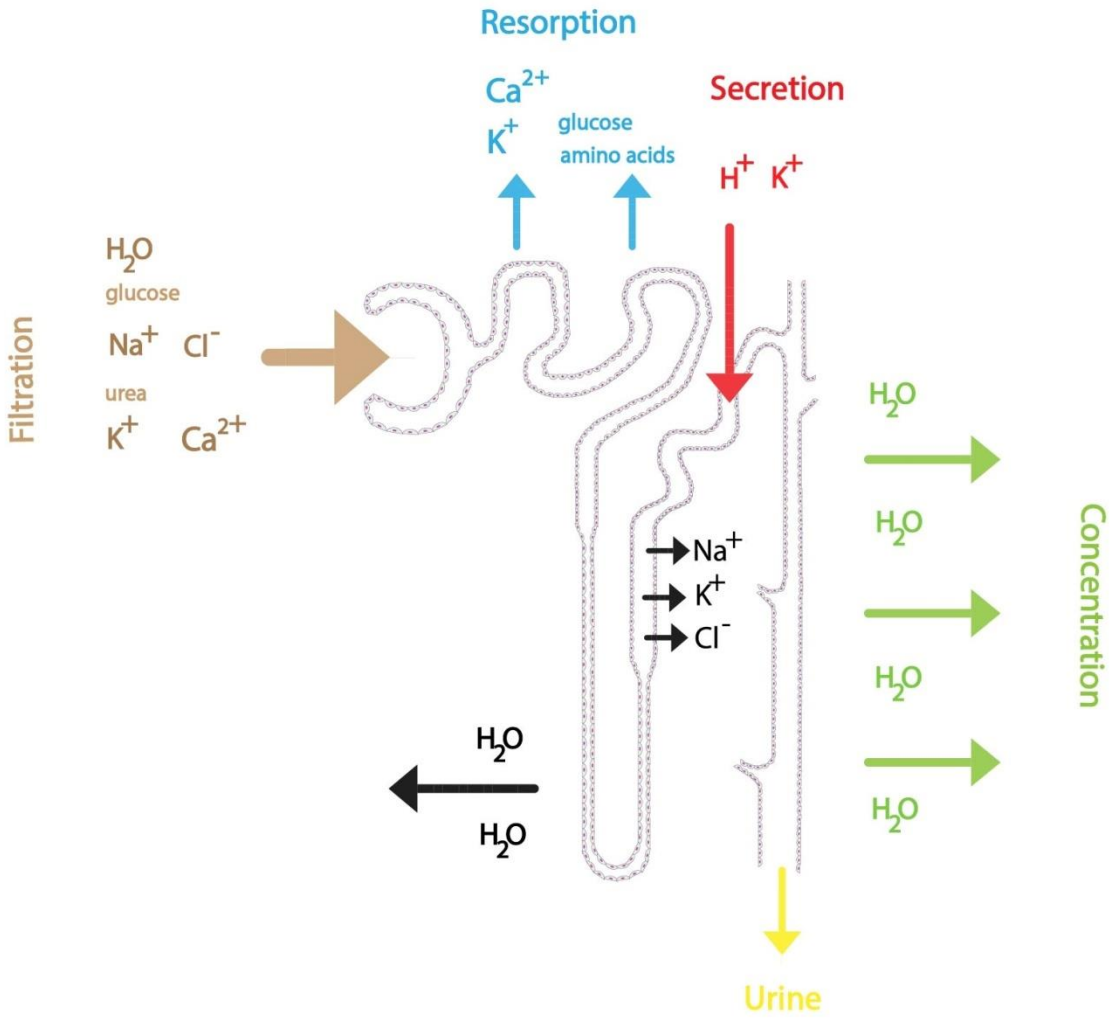
$P_{ef} = P_g – (P_{PP} + P_{BC})$

$\therefore P_{ef} = 74 – (30 + 20)$ mm of Hg

$\therefore P_{ef} = 24$ mm of Hg.

Thus, by substituting the normal values of the various forces, it has been found that the calculated effective (net) filtration pressure (P_{ef}) is 24 mm Hg.

Tubular Reabsorption



From the Bowman's capsule, the glomerular filtrate enters the proximal convoluted tubule. Absorption of selected materials takes place from the filtrate into the blood of the peritubular capillaries or vasa recta. It is termed the tubular reabsorption.

Reabsorption involves both passive and active transport across the tubular epithelium. As already stated, the glomerular filtrate in the Bowman s capsule resembles blood plasma in composition except for plasma proteins and fats. Therefore, it is almost isotonic to the plasma.

The rate of formation of the primary urine is 120 ml/minute, while the rate of urine passing to the bladder under the same condition is 1-2 ml/ minute. Therefore, it indicates that about 99 per cent of the glomerular filtrate is reabsorbed during its passage through the different segments of the renal tubule.

Transport can be carried by **passive diffusion** (in the direction of the concentration or electrical gradient), **primary active transport** against gradient (needs energy – ATP) or **secondary active transport** (transport protein uses the concentration gradient created by a primary active transport realized by other transport protein). Substances can be transported by **paracellular** or **transcellular** routes. Transport of water is always passive. **Na^+/K^+-ATPase** located on the basolateral membrane plays important role in the secondary active transport. It creates a concentration gradient for Na^+.

Transport proteins act as symporters (transport of compound is coupled to the transport of Na^+ in the same direction) or antiporters (transport of compound is coupled to the transport of Na^+ in the opposite direction). To understand the processes in the tubular system, we must imagine tubular epithelial cells, their **apical membrane** facing the **tubular fluid** (primary urine), basolateral membrane, on the other hand, is in contact with the **peritubular fluid** (here is located the Na^+/K^+-ATPase).

Although, the glomerular filtrate contains nearly the same concentration of glucose as in plasma, the urine contains nil or very little glucose. Hence, glucose is also practically completely reabsorbed in the tubules when the blood sugar level is normal. The capacity of reabsorption depends on the renal threshold of that substance.

(i) Proximal Convoluted Tubule (PCT):

About 65 per cent of the glomerular filtrate is normally reabsorbed in the proximal convoluted tubule before reaching the loop of Henle. Glucose, amino acids, vitamins, hormones, sodium, potassium, chlorides, phosphates, bicarbonates, much of water and some urea from the filtrate are absorbed.

Sulphates and creatinine are not reabsorbed. Sodium and potassium are reabsorbed by primary active transport. Glucose and amino acids are reabsorbed by secondary active transport. Water is reabsorbed by osmosis. Chloride ions, urea and other solutes are reabsorbed by diffusion. The filtrate is isotonic to blood plasma.

Reabsorption of sodium ions is in the **first half of the proximal tubule** coupled with the reabsorption of bicarbonate, glucose, amino acids, lactate, urea and phosphate. Absorbed compounds are osmotically active, thereby **draining water from tubules**. This leads to an increased concentration of chloride ions in the tubular fluid that is very important for a reabsorption in other parts of the proximal tubule.

[NOTE:

Reabsorption of bicarbonate ions in the proximal tubule

Movement of **bicarbonate** and **hydrogen ions** depends on the transport sodium ions. This process is catalyzed by enzyme **carbonic anhydrase** (located in the apical membrane and in the intracellular part of the epithelial cells). The first step is the secretion of H^+ into the tubular fluid through the **Na^+/H^+ antiport**, located at the luminal (apical) membrane of proximal tubule cells. Transferred H^+ may in the tubular fluid react with filtered bicarbonate ions to form carbonic acid. **Carbonic anhydrase** facilitates the decomposition of carbonic acid in the tubular fluid to water and carbon dioxide. Both compounds can freely **diffuse** into the tubule epithelial cells, where carbonic acid is restored by the carbonic anhydrase. Molecules of carbonic acid **dissociates** into hydrogen and bicarbonate ions. Bicarbonate ions then pass through the basolateral membrane into the interstitial fluid through **$Na^+/3HCO_3^-$-cotransporter** or **anion exchanger** (Cl^-/HCO_3^-). H^+ returns via antiport with Na^+ into the tubular fluid. For each secreted H^+, Na^+ and HCO_3^- is absorbed (Na^+ is returned to the blood by active transport in exchange for K^+ – **Na^+/K^+-ATPase**).]

Sodium, chloride, and bicarbonate are reabsorbed uniformly along the entire length of the proximal tubule and also in the distal tubule. Potassium is reabsorbed in the proximal and secreted in the distal tubule.

The glomerular filtrate produces about **170 litres in a day**; whereas the tubules reabsorb about 168.5 litres of water, 170 gm of glucose, 100 gm of NaCl, 360 gm of $NaHCO_3$, and small amounts of phosphate, sulphate, amino acids, urea, uric acid, etc. and excrete about 60 gm of NaCl, urea and

other waste products in about **1.5 litres of urine**. Most of these solids are reabsorbed by active transport mechanism, while some (e.g., urea) are reabsorbed by passive transport mechanism.

In diseases, the reabsorption mechanism is altered developing glycosuria, phosphaturia, and amino aciduria.

(ii) Loop of Henle:

It consists of descending limb and ascending limb.

(a) Descending limb of loop of Henle:

As the filtrate flows in it, its water is reabsorbed due to increasing osmolality of interstitial fluid. Sodium and other solutes are not reabsorbed here. The filtrate becomes hypertonic to blood plasma.

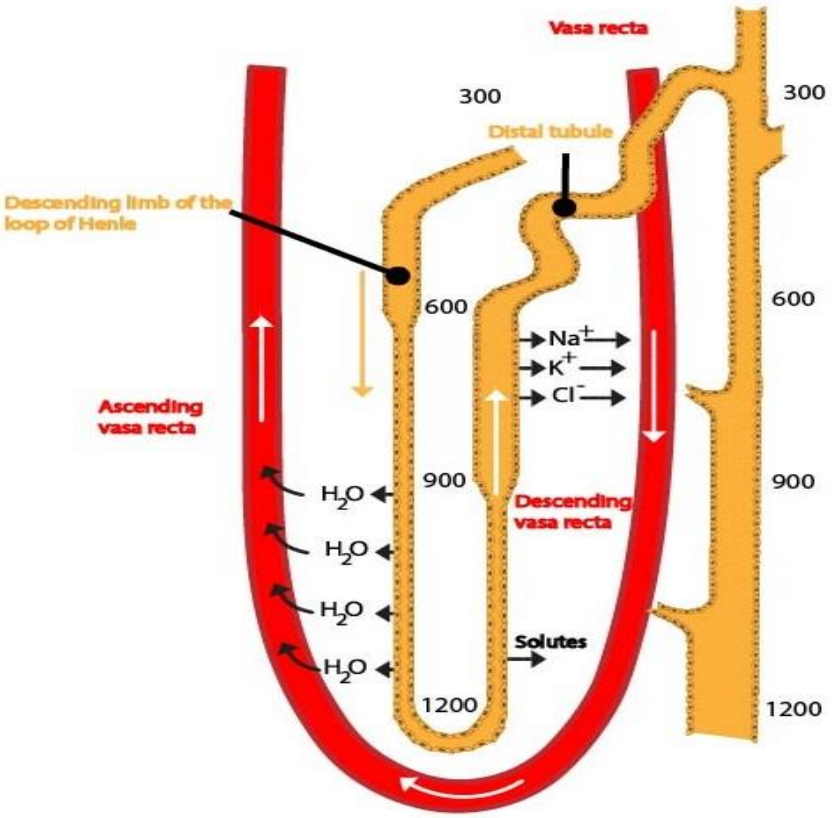
(b) Ascending limb of loop of Henle:

It **is impermeable to water but permeable to K^+, Cl^- and Na^+ and partially permeable to urea**. Thus in the thick ascending limb of the loop of Henle sodium, potassium, calcium, magnesium, and chloride are reabsorbed. The filtrate becomes hypotonic to blood plasma.

Mechanism of urine concentration in Loop of Henle

Henle's loop absorbs about 25 % of the solutes (thick segment of the ascending limb), but only about 15 % water (descending limb). Its proper function (thick part of the ascending limb is impermeable to water and has active transport of Na^+ and Cl^-) is essential for the **formation of a high osmotic pressure** (**hyperosmolarity**) **in the renal medulla** that ensures a production of highly concentrated urine. Some mechanisms of reabsorption of ions are similar to those in the proximal tubule.

Very important is the specific symport of Na^+, K^+ and 2 Cl^- across the apical membrane. This symport uses energy derived from the transport of sodium and chloride ions in the direction of their concentration gradient for the transport of potassium ions into the cell (against their concentration gradient). Some of these ions leave cells on the basolateral membrane (together with Cl^-), some return back into the tubular fluid, thereby creating an electrical imbalance. Due to this, positively charged ions (Na^+, K^+, Ca^{2+}, Mg^{2+}) are resorbed by **paracellular route** (very important mechanism for reabsorption of solutes). This is especially significant for formation of a **hypertonic** (concentrated) renal medulla. **Hypotonic fluid** (dilute) leaves the loop of Henle and enters the distal tubule.



Concentration of urine with help of peritubular capillaries

(iii) Distal convoluted tubules (DCT) and Collecting Duct:

Distal convoluted tubule and collecting duct resorbe about **7 % of solutes** (mainly Na^+ and Cl^-) and approximately **17 % water**. Their reabsorption is **affected by hormones** (e.g. ADH) – **facultative reabsorption**. Hydrogen and potassium ions are secreted here. The distal convoluted tubule and the collecting duct thus play an important role in the formation of the final urine and in the regulation of osmolarity and pH. Sodium and chloride ions are absorbed in the first part of the distal convoluted tubule.

The distal part of the distal convoluted tubule and the collecting duct consist of two cell types:

1) Principal cells responsible for the reabsorption of sodium ions and water (dependent on ADH) and secretion of K^+ ions

2) Intercalated cells containing carbonic anhydrase. They are involved in acid-base balance, because they can secrete both hydrogen and bicarbonate ions

This makes the filtrate isotonic to blood plasma.

From distal convoluted tubule filtrate enters the collecting duct where further reabsorption of water takes place. Now the filtrate becomes more concentrated which makes filtrate hypertonic to blood plasma. The entire duct is permeable to water.

Thus a considerable amount of water is reabsorbed in the collecting duct under the influence of ADH. Sodium is reabsorbed in the collecting duct under the influence of aldosterone. The filtrate is now called urine. Thus urine is hypertonic to blood and isotonic to medullary fluid.

Tubular Secretion:

The cells of the renal tubule not only remove substances from the filtrate by the process of reabsorption and send them to the blood capillaries (peritubular) but also excrete additional wastes from the blood stream into the filtrate by the process of secretion. Thus tubular secretion is the opposite of tubular reabsorption.

(i) Creatinine, hippuric acid, pigments, drugs including penicillin are actively secreted into the filtrate in the proximal convoluted tubule from the interstitial fluid. Hydrogen ions and ammonia are also secreted into the proximal convoluted tubule.

(ii) Urea enters the filtrate by diffusion in the thin segment of the ascending limb of loop of Henle.

(iii) Potassium, hydrogen ions, ammonia, HCO_3^- ions are secreted by active transport into the filtrate in the distal convoluted tubule.

Maximum hydrogen secretion occurs in the proximal convoluted tubule. Removal of hydrogen ions and ammonia from the blood in the proximal convoluted tubule and distal convoluted tubule helps to maintain the pH of the blood between 6 to 8 (pH of blood is usually 7.4).

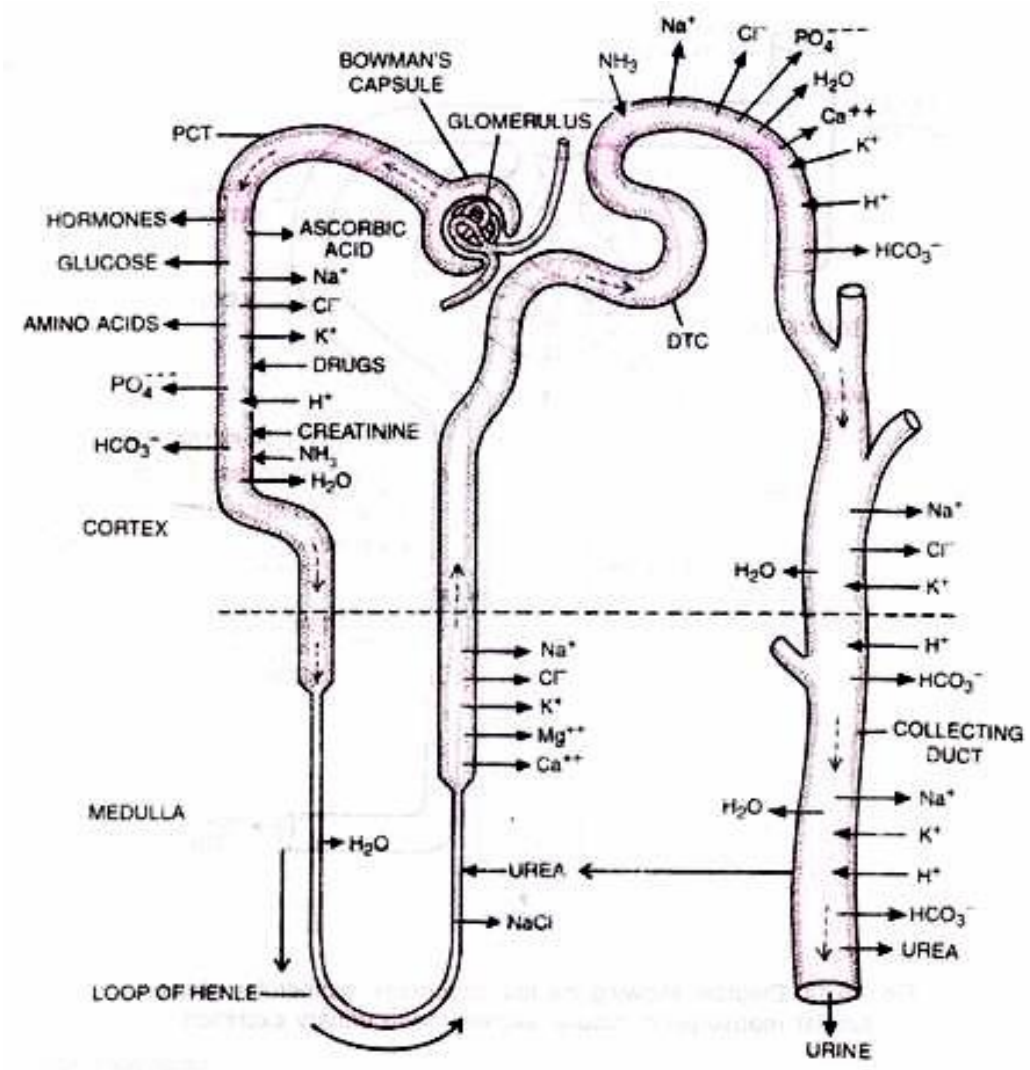


Image showing details of substances reabsorbed and secreted in the nephron

Hormonal regulation:

The function of kidney is regulated by three important hormones. These hormones are aldosterone (from adrenal cortex), Angiotensin II (from kidney), and vasopressin or ADH (from hypophyseal posterior lobe).

Aldosterone is secreted by the **zona glomerulosa** of the **adrenal cortex** in response to increasing plasma concentrations of **angiotensin II** and **potassium ions**. It plays therefore an important role in maintaining of constant level of potassium ions (**accelerates secretion** of potassium ions in the thick segment of the loop of Henle and in the distal tubule) and in **regulation of volume of ECF**. As the part of the **renin-angiotensin-aldosterone system**, it **stimulates reabsorption of sodium ions**, accompanied by **passive water reabsorption** (distal tubule and collecting ducts). This system is activated by decrease in the plasma volume.

ADH (antidiuretic hormone, vasopressin) is produced in the **hypothalamus** and secreted by the **posterior pituitary gland** in a response to an **increased osmolarity of extracellular fluid** (to a lesser extent as an answer to a decrease of extracellular fluid volume). ADH binds to the **V_2-receptor** located on collecting duct cells (partly on distal tubule cells). Its effect increases the number of **aquaporins** in cell membranes and water molecules can pass along the osmotic gradient into peritubular fluid (ECF). ADH acts also on a **transport of urea** in the collecting duct and on a transport of Na^+ and Cl^- in the thick segment of the ascending limb of the loop of Henle.

Angiotensin II stimulates aldosterone secretion and reabsorption of sodium ions (and consequently reabsorption of water molecules) in the proximal tubule.

REGULATION OF ACID-BASE BALANCE

Proper physiological functioning depends on a very tight balance between the concentrations of acids and bases in the blood. Acid-balance balance is measured using the pH scale. A variety of buffering systems permits blood and other bodily fluids to maintain a narrow pH range, even in the face of perturbations. A buffer is a chemical system that prevents a radical change in fluid pH by dampening the change in hydrogen ion concentrations in the case of excess acid or base. Most commonly, the substance that absorbs the ions is either a weak acid, which takes up hydroxyl ions, or a weak base, which takes up hydrogen ions.

The buffer systems in the human body are extremely efficient, and different systems work at different rates.

It takes only seconds for the chemical buffers in the blood to make adjustments to pH.

The respiratory tract can adjust the blood pH upward in minutes by exhaling CO_2 from the body.

The renal system can also adjust blood pH through the excretion of hydrogen ions (H^+) and the conservation of bicarbonate, but this process takes hours to days to have an effect.

Renal Regulation of Acid-Base Balance

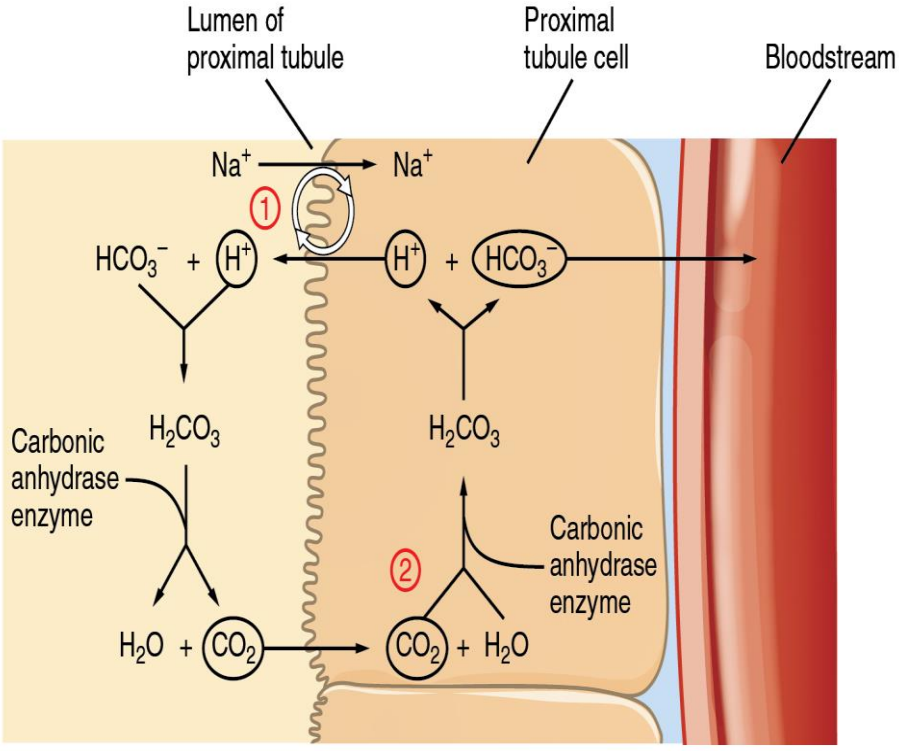
The kidneys help maintain the acid–base balance by excreting hydrogen ions into the urine and reabsorbing bicarbonate from the urine. The kidneys take part in maintaining the acid-base balance by means of:

1) Reabsorbing, excreting and producing bicarbonate

2) Excreting or producing H^+

Bicarbonate ions, HCO_3^-, found in the filtrate, are essential to the bicarbonate buffer system, yet the cells of the tubule are not permeable to bicarbonate ions. The steps involved in supplying bicarbonate ions to the system are seen in the figure and are summarized below:

- Step 1: Sodium ions are reabsorbed from the filtrate in exchange for H^+ by an antiport mechanism in the apical membranes of cells lining the renal tubule.
- Step 2: The cells produce bicarbonate ions that can be shunted to peritubular capillaries.
- Step 3: When CO_2 is available, the reaction is driven to the formation of carbonic acid, which dissociates to form a bicarbonate ion and a hydrogen ion.
- Step 4: The bicarbonate ion passes into the peritubular capillaries and returns to the blood. The hydrogen ion is secreted into the filtrate, where it can become part of new water molecules and be reabsorbed as such, or removed in the urine.



Bicarbonate (HCO_3^-) does not have a transporter, so its reabsorption involves a series of reactions in the tubule lumen and tubular epithelium. In response to acidosis, the tubular cells reabsorb more bicarbonate from the tubular fluid, and the collecting duct cells secrete more hydrogen and generate more bicarbonate, and ammoniagenesis leads to an increase in the formation of the NH_3 buffer.

In response to alkalosis, the kidneys may excrete more bicarbonate by decreasing hydrogen ion secretion from the tubular epithelial cells, and lowering the rates of glutamine metabolism and ammonium excretion.

You should notice that loss of bicarbonate is **the same as** acquiring of H^+ and production of bicarbonate is **the same as** loss of H^+.

These processes are connected (e.g. excretion of H^+ in proximal tubule is connected with reabsorption of HCO_3^- in the same place or excretion of H^+ in distal tubule is connected with production of HCO_3^- in the same place). Thus, **higher bicarbonate concentration** increases pH, **lower bicarbonate concentration** decreases pH.