CHAPTER - 1

THE EXCRETORY SYSTEM

Introduction

- Kidneys are the principal excretory organ of human excretory system. It is found in a pair and each is located in retroperitoneal position, i.e. between 12th thoracic vertebra and 3rd lumbar vertebra, close to dorsal inner of abdominal cavity and not inside it.

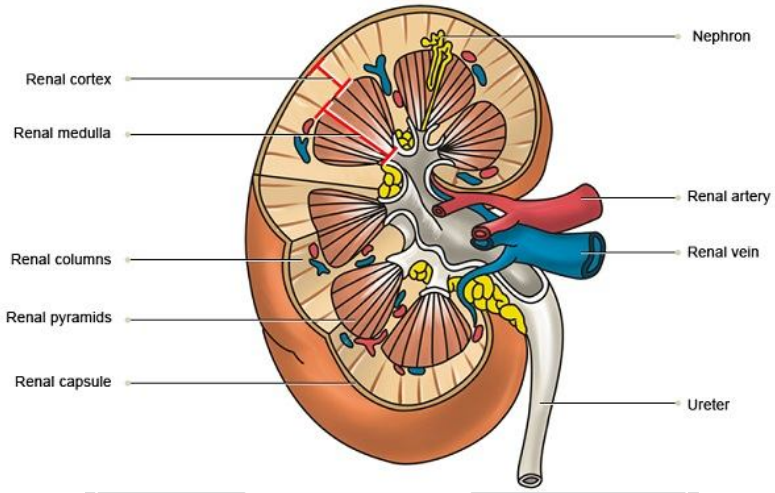

FIGURE : STRUCTURE OF KIDNEY

- **Functions of kidney can be summed up as below :**
  1. Excretion of metabolic waste products and foreign chemicals.
  2. Regulation of water and electrolyte balances.
  3. Regulation of body fluid osmolarity and electrolyte concentrations.
  4. Regulation of arterial pressure.
  5. Regulation of acid-base balance.
  6. Secretion, metabolism and excretion of hormones.

  The structure and functions of kidneys are discussed below in required detail.

- **Nephron :** It is the structural and functional unit of kidney.

(1) Structure of nephron : It has many different regions in two categories i.e., glomerulus and renal tubule. These are explained below.

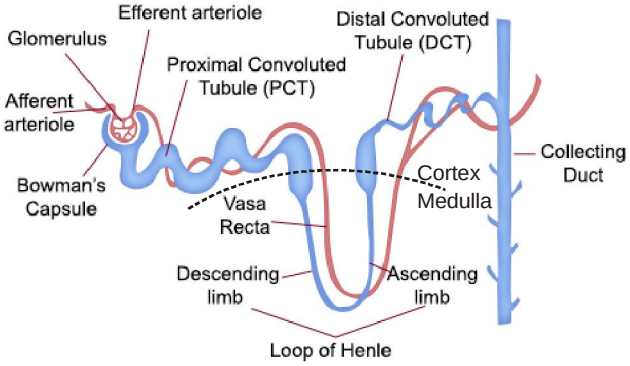

FIGURE : STRUCTURE OF NEPHRON

- **Glomerulus :** It is the capillary bed connecting afferent and efferent renal arteriole. It is found in renal cortex and is surrounded completely by blind end of nephron called Bowman's capsule.
- **Bowman's capsule :** It covers glomerulus completely and provides interface between blood and renal filtration apparatus.
  - It is made up of modified simple squamous epithelium cells called podocytes. These help during ultrafiltration process.
  - It is found in renal cortex.
- Malpighian capsule = Glomerulus + Bowman's capsule (Glomerular capsule).
- **Renal tubule :** It is part of nephron beyond Bowman's capsule till end of collecting duct.
  - **It has many subparts with specialized functions. These are :**

(A) Proximal Convoluted Tubule (PCT) : It is part of renal tubule just beyond Bowman's capsule, so called PCT.
- It is found in renal cortex.
- It is lined with simple cuboidal brush border epithelium which increases the surface area of absorption.
- It is main site of solute reabsorption from renal filtrate.

(B) Loop of Henle : It is a U-shaped part of tubule and connects PCT with DCT.
- It is found in renal medulla. Based on its length in renal medulla, nephrons are of two types :

(i) Cortical nephrons : Loop of Henle is very short and dips only slightly in medulla. About 70 % of nephrons.

(ii) Juxtamedullary nephrons : Loop of Henle is very long and runs deep into medulla. About 30 % of nephrons.
- Loop of Henle has a descending limb, a thin ascending limb and thick ascending limb.
- The thick ascending limb connects to DCT. Just before, DCT, it has a specialized area called macula densa that is part of juxta-glomerular apparatus.
- Loop of Henle primarily functions in filtrate concentration and osmolarity regulation.

(C) Distal convoluted tubule (DCT) : It opens into collecting duet and is found in renal cortex.
- It is lined by simple cuboidal epithelium.
- It is important in conditional absorption of water, Na^+, HCO_3^- and secretion of H^+, K^+ and NH_4^+ and NH_3. Thus, it is important for maintenance of pH in blood and body.

(D) Collecting duct : It is last part of nephron.
- It extends from renal cortex deep into renal medulla.
- It is lined by simple cuboidal epithelium cells of two types :
  1. **Intercalated cells :** They are involved in urine acidification and acid base balance.
  2. **Principal cells :** They are involved in Na^+ reabsorption and maintenance of extracellular fluid volume.
- It is site of final concentration of urine via water reabsorption.

(2) Functions of nephron : Nephron performs 3 functions viz. (I). urine formation, (II). osmoregulation, (III). Acid-base balance. These are discussed below.

(I) Urine formation : It is required for excretion of metabolic waste products in blood. This happens in 3 steps.
- **Glomerular filtration :** It is the first step and involves filtration of blood by glomerulus. The glomerular capillary pressure cause blood filtration across 3 layers.
  (i) Endothelium of glomerular blood vessels.
  (ii) Endothelium of Bowman's capsule.
  (iii) Basement membrane between them.
- Endothelial cells of Bowman's capsules are called podocytes.
- These are arranged so as to have minute pores called filtration or slit pores.

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- The blood is filtered through all these membranes very finely, so that, nearly all constituents of plasma except proteins pass into lumen of Bowman's capsule. Due to this finese, it is called ultrafiltration.

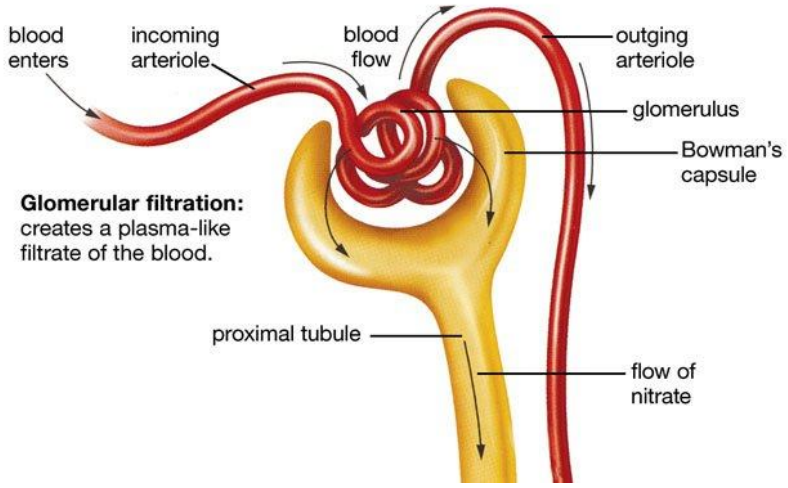

FIGURE : ULTRAFILTRATION

- A healthy kidney filters 1100 – 1200 ml of blood/minute.
- The amount of filtrate formed by kidneys/ minute is called glomerular filtration rate (GFR). (GFR) is calculated as :

  GFR = K_f × Net filtration pressure. Here,

  K_f = glomerular capillary filtration constant in per 100 gm of kidney.

  Net filtration pressure = sum total of filtration promoting and filtration opposing forces. Its normal value is +10 mm of Hg.
- GFR is regulated by Juxta-glomerular apparatus (JGA) coupled with renin-angiotensin system.
- Clinically, GFR is measured by creatinine clearance rate.

➢ **Reabsorption and secretion :** These 2 steps follow ultrafiltration.

- The efferent arteriole emerging from glomerulus form a fine capillary network around the renal tubule, called peritubular capillary network.
- Reabsorption is movement of solute and water from lumen of renal tubule to peritubular capillaries. To undergo reabsorption, a substance must be transported across renal tubular epithelial membranes.
- Secretion is movement of metabolic waste, excess solute ions etc. from peritubular capillaries to lumen of renal tubule.

➢ Different parts of renal tubule show different reabsorption and secretion characteristic and are described below.

(A) Proximal convoluted tubule (PCT) : It has a brush border epithelium and is a major site of reabsorption.

- All the essential nutrients (glucose, amino acids etc.) , 80% of electrolytes (Na^+, Cl^- etc.) and water are reabsorbed.
- Water reabsorption in PCT is facililated by constitutive expression of water absorption chamels AQP-1 and AQP-7.
- PCT also helps maintain pH and ionic balance of body fluids. It does so by reabsorbing HCO_3^- from filtrate and selective secretion of H^+, NH_4^+ and K^+ ions into filtrate.

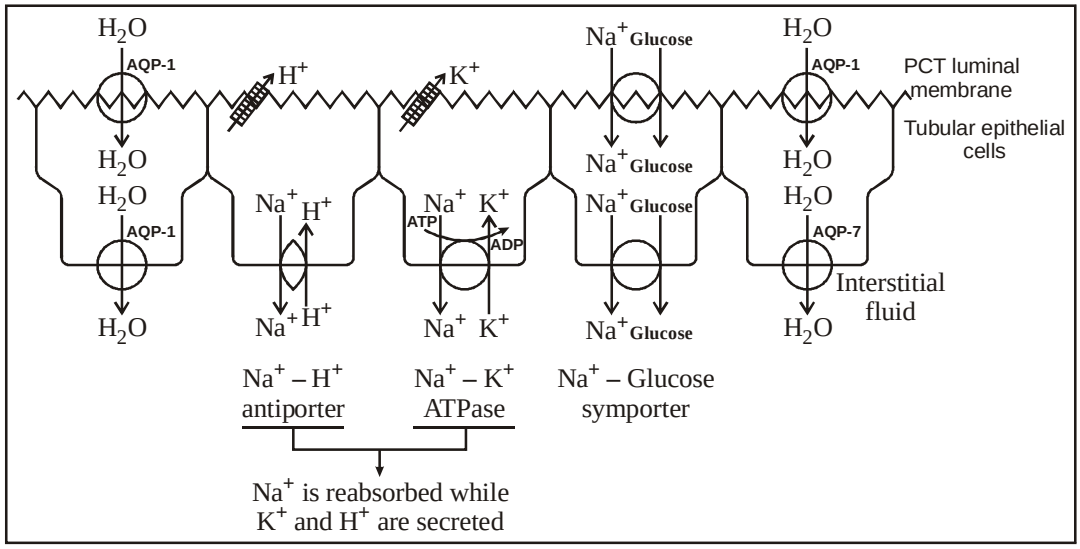

FIGURE : REABSORPTION AND SECRETION IN PCT OF RENAL TUBULE

(B) Henle's Loop : Reabsorption in different regions is as under :

- Descending limb of Henle's loop is permeable to water and impermeable to electrolytes. Thus, water is reabsorbed and filtrate is concentrated. This filtrate enters ascending thin limb of Henle's loop.
- Thin ascending limb is permeable to Na^+, Cl^- and urea but impermeable to water. Thus, solutes are reabsorbed and filtrate gets diluted moving up into thick ascending limb.
- Thick ascending limb too is permeable to Na^+, Cl^- but not urea and water reabsorption. Thus, filtrate gets hyposmotic (150 m Osm/L) relative to initial filtrate (300 m Osm/L).

(C) Distal convoluted tubule (DCT) : In this, conditional reabsorption of Na^+, Cl^-, HCO_3^- and H_2O takes place.

- The Na^+ and Cl^- uptake is helped by $Na^+ – Cl^-$ symporter and $Na^+ – K^+$ ATPase.
- Parathyroid hormone (PTH) acts on DCT to stimulate reabsorption of Ca^{2+}.
- H^+, K^+, NH_3 and NH_4^+ are secreted in this region to maintain pH and $Na^+ – K^+$ balance in blood.

(D) Collecting duct (CD) : It is the last part of nephron and made up of principal and intercalated cells.

- Principal cells reabsorb Na^+ and secrete K^+. This activity is regulated by hormone aldosterone.
- Intercalated cells actively secrete H^+ ions into tubular lumen using H^+-ATPase transporter.
- CD is where urine is finally concentrated. This process is effected by hormone anti-diuretic hormone (ADH) or vasopressin.
- ADH acts on principal cells and upregulates the expression of AQP-2 water absorption channel on the luminal membrane of CD.
- Maximum reabsorption, secretion and concentration of urine happens in the inner medullary portion of CD, just before it empties into renal pelvis.

  This whole process of urine formation can be summed up in following figure.

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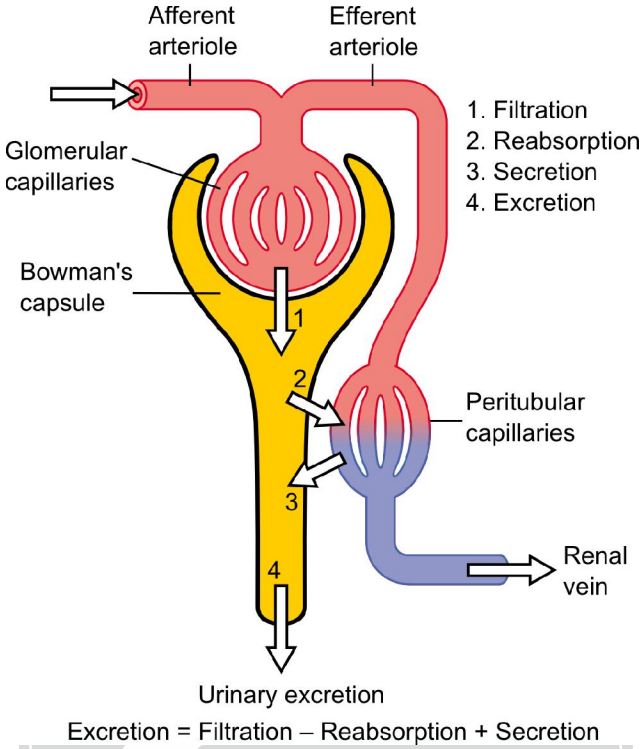

FIGURE : SUMMARY OF URINE FORMATION

♦ **Counter current mechanism for filtrate concentration :**

- The efferent arteriole emerging from glomerulus forms a fine capillary network around renal tubule, called, peritubular capillary network.
- A minute vessel of this network runs parallel to Henle's loop, forming a U-shaped vasa recta. This vasa recta-Henle loop system, in juxta-medullary nephrons, is important in formation of concentrated urine and osmoregulation. This is explained in following points.
- The flow of filtrate in two limbs of Henle's loop is in opposite directions and thus, forms a counter current.
- The flow of blood through the two limbs of vasa recta is also in counter current pattern.
- The proximity between Henle's loop and vasa recta, as well as counter current in them, helps in maintaining an increasing osmolarity from cortex towards inner medullary interstitium.
-

Region	Cortex	Outer medulla	Inner medulla
Osmolarity (m Osm/L)	300	600	1200

- This gradient is maintained mainly by NaCl and urea.
- NaCl is transported from ascending thick limb of Henle's loop into descending limb of vasa recta. The route is – thick ascending limb of Henle's loop $\xrightarrow{NaCl}$ Interstitium $\xrightarrow{NaCl}$ descending limb of vasa recta.
- This NaCl is returned to the interstitium by ascending portion of vasa recta.
- Similarly, small amounts of urea enter the thin ascending limb of Henle's loop and is transported back to interstitium by collecting duct. The route is
  CD $\xrightarrow{urea}$ renal interstitium in inner medulla $\xrightarrow{urea}$ ascending thin limb of Henle's loop $\xrightarrow{urea}$ CD.
- This above described transport of substances facilitated by the special arrangement of Henle's loop and vasa recta is called as counter current mechanism. It is shown in figure below.

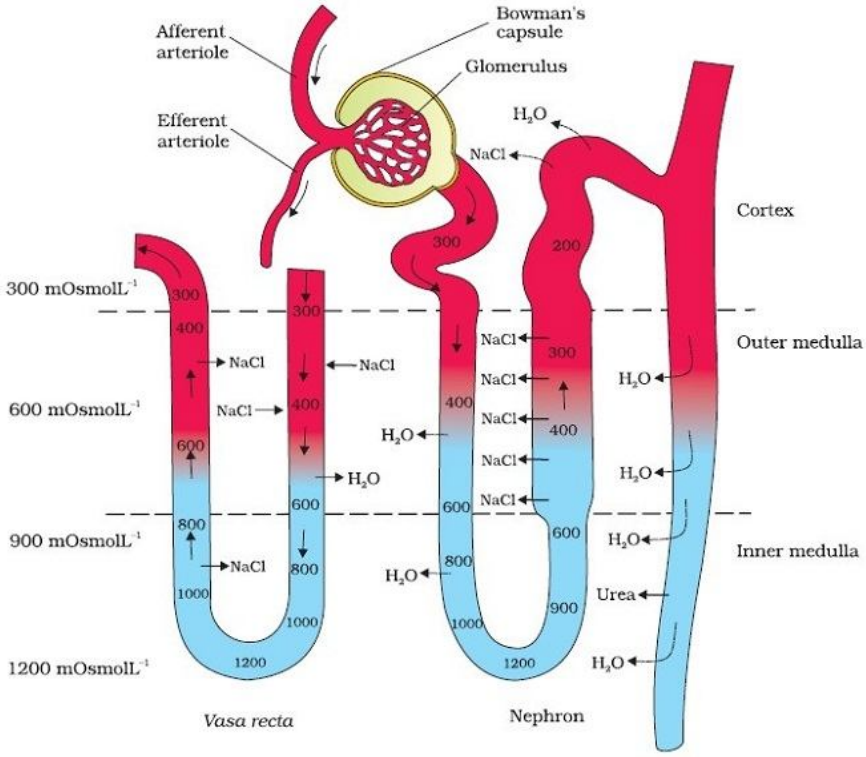

FIGURE : COUNTER CURRENT MECHANISM

- This mechanism helps maintain a concentration or osmotic gradient in the medullary interstitium.
- This osmotic gradient helps in easy passage of H_2O from collecting duct.
- This reabsorption of water facilitated by counter-current mechanism helps in concentrating urine and osmoregulation by maintaining homoeostatic water volume in body.

♦ **Osmoregulation : Regulation of electrolytes in body fluids :**

- Though counter current mechanism alongwith reabsorption and secretion in renal tubule are important in maintaining extracellular fluid volume and electrolyte balance in body.
- However, there are some important processes specialized for electrolyte regulation. These are described below.

➢ **Sodium :** Na^+ is most abundant cation in extracellular fluid. Its level is blood plasma is controlled by

- **Aldosterone :** It increases renal reabsorption of Na^+.
- **Antidiuretic hormone (ADH) :** ADH secretion is inhibited in hyponatrimia i.e., $[Na^+] < 135$ mEq/L. Thus, more water is secreted in urine and normal $[Na^+]$ in ECF is maintained.
- **Antinatriuretic peptide (ANP) :** It increases Na^+ excretion in urine under hypernatrimia.

➢ **Chloride :** Cl^- is most abundant anion in ECF. It is reabsorbed or secreted by Cl^- leakage channels or symporters.

- Its reabsorption and secretion kinetics is govered by factors affecting Na^+ retention or excretion. This is to maintain electrical neutrality.

➢ **Potassium :** K^+ is most abundant cation in intracellular fluid.

- Its blood plasma concentration is low (3.5 – 5.0 mEq/L) and is controlled by aldosterone.
- More K^+ in plasma → more aldosterone → principal cells in CD secrete excess K^+ in urine. The vice-versa is also true.

➢ **Bicarbonate :** HCO_3^- is second most abundant anion in plasma.

- Its some regulation happens during pulmonary respiration but kidneys are main regulators of blood $[HCO_3^-]$.
- Intercalated cells in CD and epithelial cells in PCT of renal tubule absorb HCO_3^-.
- Intercalated cells can secrete HCO_3^- if plasma levels are high.

➢ **Calcium :** Its reabsorption and secretion in renal tubules is governed by parathyroid hormone (PTH).

- PTH acts on distal convoluted tubule (DCT) to enhance Ca^{2+} reabsorption from glomerular filtrate.

➢ **Phosphate :** Its plasma levels are governed by factors regulating [Ca^{2+}] in plasma.

- PTH inhibits absorption of PO_4^{3-} in renal tubules and increases its excretion in urine.

➢ **Magnesium :** PTH is main regulator for retention of Mg^{2+}.

- Kidney increases urinary excretion of Mg^{2+} in hypercalcemia, hypermagnesia, increase in ECF volume and decrease in PTH levels and acidosis.
- Opposite conditions decrease renal excretion of Mg^{2+}.

♦ **Juxtaglomerular apparatus (JGA) :** JGA is located in the renal cortex.

- It is a unique segment of nephron where the thick ascending limb of Henle's loop passes between the afferent and efferent arterioles of its own glomerulus.
- Macula densa is a specialized area of the thick ascending limb that contacts the vascular elements in JGA.
- These vascular elements contain modified smooth muscle cells in arterioles, called granular cells. These cells synthesize and secrete renin enzyme.
- In addition, JGA also contains cells that synthesize and secrete renin enzyme. These cells are called lacis cells or extraglomerular mesangial cells.
- JGA plays an important role in regulation of renal function by modulations in renin-angiotensin-aldosterone system, as described below.

♦ **Regulation of kidney function :** These are 2 systems that are involved. They are described below.

(1) Renin-angiotensin-aldosterone system : It is an important and complex system for control of renal functions. Its components and their interrelations are discussed below.

➢ **Renin :** It is a proteolytic enzyme, synthesized and secreted by granular and lacis cells in JGA.

- It is secreted when JGA detects.
  1. drop in glomerular blood flow.
  2. drop in glomerular blood pressure.
  3. drop in GFR.

➢ **Angiotensins :** Angiotensinogen is a glycoprotein produced in liver.

- Its synthesis and release into circulation is stimulated by angiotensin II.
- Angiotensinogen $\xrightarrow{\text{Renin}}$ Angiotensin I $\xrightarrow[\text{enzyme (ACE)}]{\text{Angiotensin converting}}$ Angiotensin II
- ACE enzyme is found in vascular epithelium and is highly expressed in lung's vasculature. Thus, entire venous system blood while passing from lungs also undergoes conversion of angiotensin I to its active form in angiotensin II.
- Angiotensin II has following functions :
  (i) It is a very potent vasoconstrictor. It acts more on the efferent arteriole than afferent arteriole. Thus, drop in blood pressure is arrested.
  (ii) Constriction of efferent arteriole reduces renal blood flow. It helps to increase tubular reabsorption.
  (iii) It stimulates zona glomerulosa of adrenal gland to secrete aldosterone.

➢ **Aldosterone :** It is a sodium retaining mineralocorticoid hormone secreted by zona glomerulosa of adrenal gland.

- It is released in response to
  (i) stimulation by angiotensin II.
  (ii) drop in [Na^+] and or rise in [K^+] in plasma.
- It acts on principal cells in CD to upregulate expression of Na^+-transporters and $Na^+ - K^+$ ATPase pump, so that, Na^+ is retained and K^+ is secreted in urine.

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- It acts on intercalated cells in CD to increase the activity of $Na^+ - H^+$ antiporter. This imports Na^+ and secretes H^+ in urine.

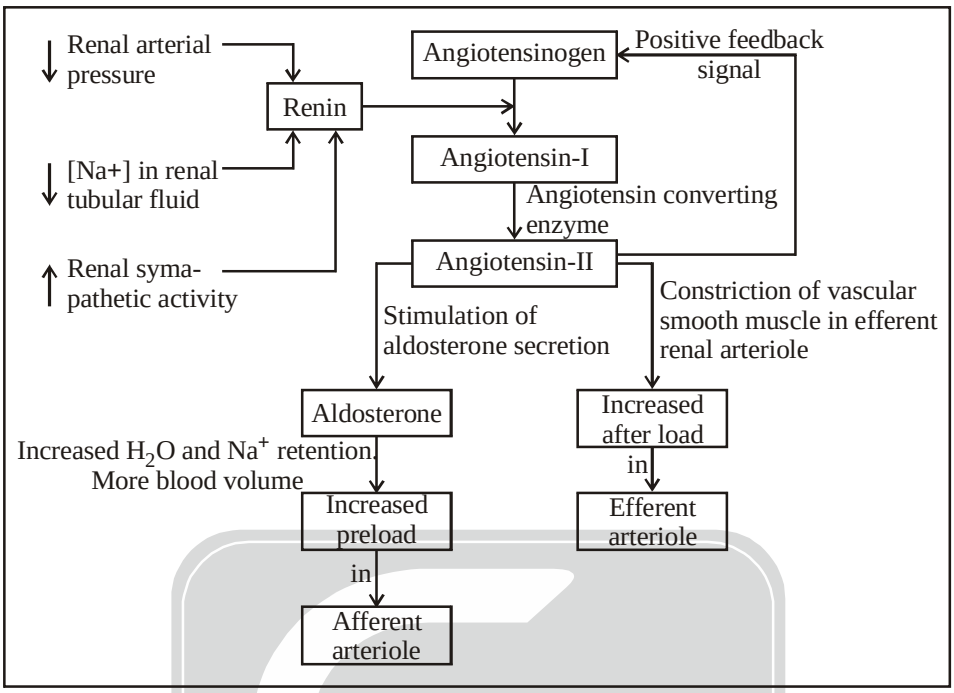

Figure : Renin-angiotensin-aldosterone system

(2) <u>Atrial natriunetic factor (ANF)</u> : It is also known as atrial natriuretic hormone (ANH) and atrial natriuretic peptide (ANP).

- It is a powerful vasodilator peptide hormone.
- It is secreted by heart muscle cells called atrial myocytes in the atria region of heart.
- It is released in response to high blood volume.
- It acts to reduce H_2O, Na^+ loads on vascular system. Thus, reduces blood pressure.
- Since, its effects are opposite of renin-angiotensin-aldosterone system. It acts as check on latter.

♦ **<u>Micturition</u> :** Urine formed by nephrons passes down ureter to be stored in urinary bladder. Capacity of bladder is 500-700 ml.

- When completely filled, its walls get stretched activating its stretch receptors.
- These receptors signal CNS and it passes the motor message to initiate contraction of smooth muscles of bladder and simultaneous relaxation of urethral sphincter, causing the release of urine.
- This process of release of urine to outside is called as micturition. The neural mechanisms causing it to happens are called micturition reflex.
- An adult human excretes 1-1.5 L of urine/day.
- Urine normally has a light yellow colour, is a watery fluid, slightly acidic (pH 6.0) with characteristic odour.
- On average 25-30 gm of urea is excreted everyday.

♦ **<u>Excretory products in humans and their formation</u> :** Humans and terrestrial mammals are mainly ureotelic i.e., excrete urea as main excretory product. But they also excrete significant amounts of uric acid and creatinine.

Formation of urea, uric acid and creatinine are described below.

(1) Formation of urea : It is required to excrete NH_3 in a non-toxic and water conserving pathway.

- Its site of formation is liver.
- When excess amino acids beyond metabolic needs are accumulated in extrahepatic tissues, they can be degraded to release NH_3, which is toxic.
- Thus, such amino acids undergo transamination reaction catalyzed by aminotransferases.

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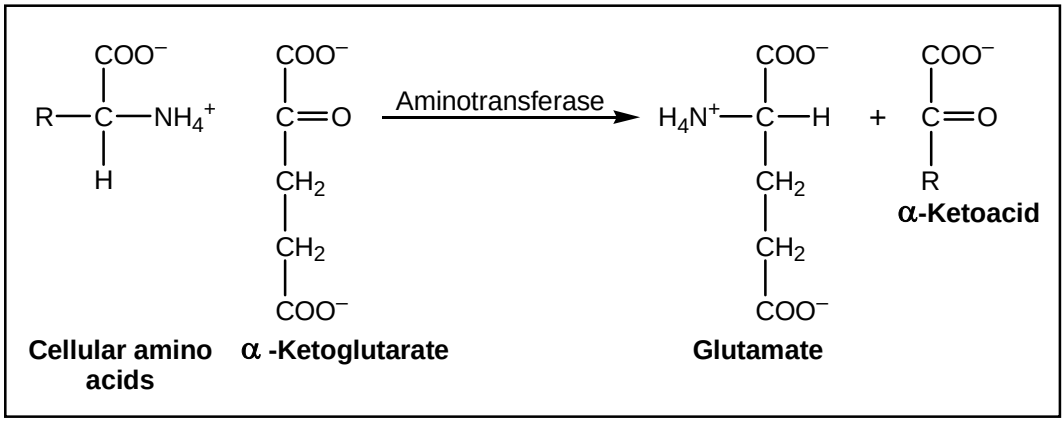


- Glutamine is transferred to liver by blood. Excess amino acid is converted to glutamate by transmination and then starts the process of urea formation. It is shown below.

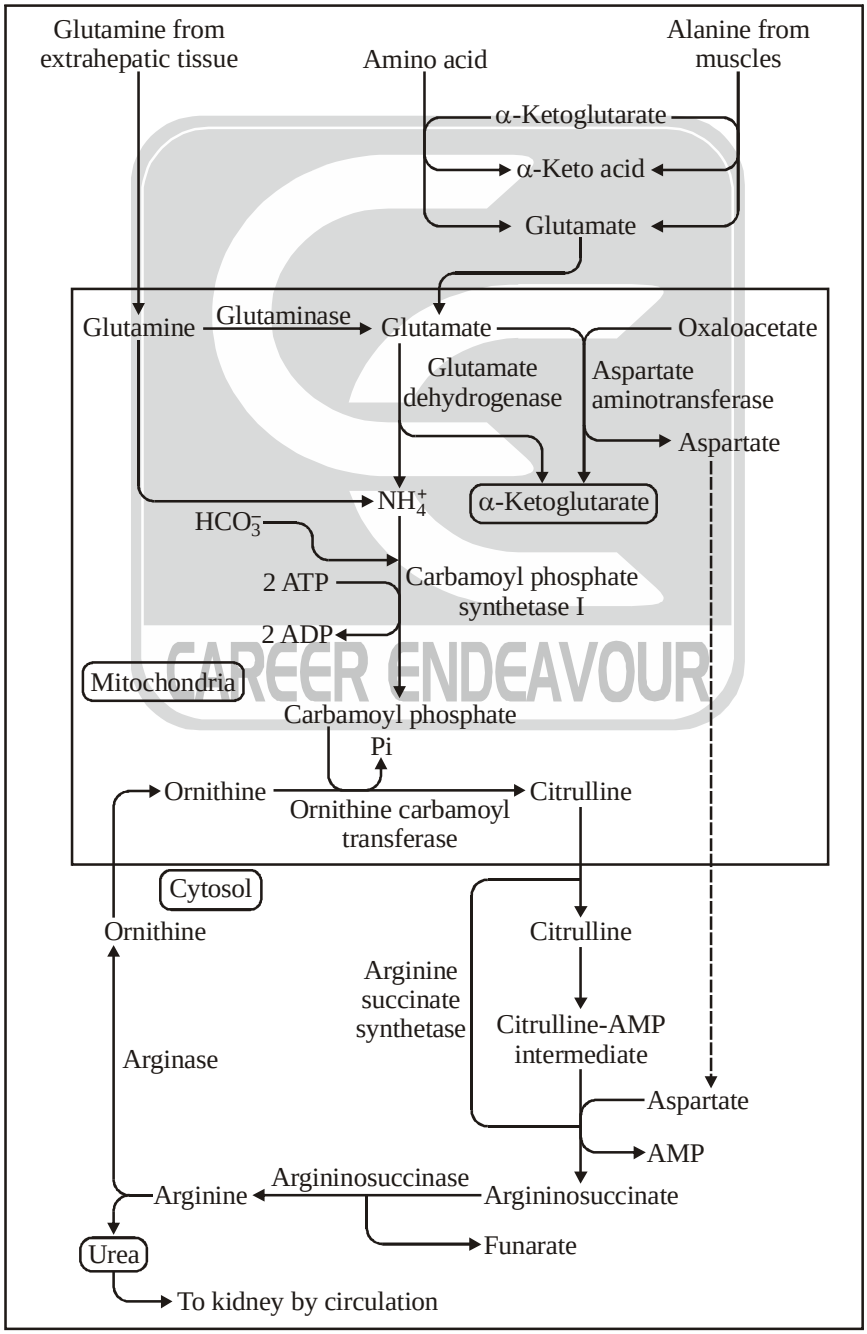
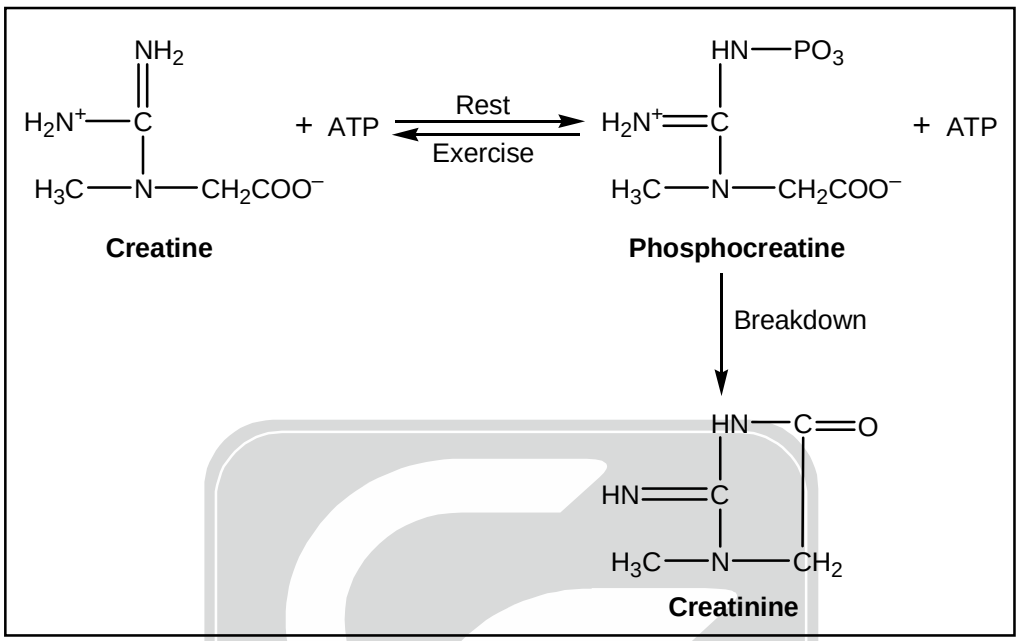


FIGURE : UREA CYCLE

- Urea cycle is also called as Kreb-Hanseleit cycle. It was discovered in 1932 by Hans Kreb and his student Kurt Hanseleit.
- In this cycle, enzyme carbamoyl phosphate synthetase I is the regulating enzyme.

(2) Formation of creatinine : Creatinine is a breakdown product of creatine phosphate in muscle. Its production is shown below :



- Creatinine is produced at an average constant rate. The rate depends on muscle mass.
- Creatinine is filtered by kidney and small amount is activity secreted.
- There is no tubular reabsorption of creatinine, therefore, if filtering of kidney is deficient, its blood levels rise.
- Thus, creatinine levels in blood and urine are used to calculate creatinine clearance rate which reflects on the GFR. GFR in turn denotes renal dysfunction.

(3) Formation of uric acid : Uric acid is formed due to metabolism of adenine and guanine based purines.

- Examples of such purine derivatives are hypoxanthine and xanthine.
- Hypoxanthine + O_2 + $H_2O \xrightarrow[\text{oxidase}]{\text{xanthine}}$ xanthine + H_2O_2.
- Xanthine + O_2 + $H_2O \xrightarrow[\text{oxidase}]{\text{xanthine}}$ uric acid + H_2O_2.
- Vegetarians have less uric acid in blood due to non-intake of purine rich meat. Excess serum accumulation of uric acid leads to a type of arthritis called gout.

♦ **Additional information about excretory system**

- **Role of other organ in excretion :** Other than kidneys following organs also contribute to elimination of excretory wastes.
- **Lungs :** They remove large amount of CO_2. 18L/day.

  They remove large amount of water too.
- **Liver :** The largest gland of body secretes bile. Bile contains substances like bilirubin, biliverdin, cholesterol, degraded steroid hormones, vitamins and drugs.

  Most of these substances pass out alongwith digestive waste.

Skin

- It contains sweat and sebaceous gland.
- Sweat contains NaCl, small amounts of urea and lactic acid. Thus, it excretes them.

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- Sebaceous glands produce sebum. It contains sterols, hydrocarbons and waxes. Thus, it eliminates them with sebum.
- Small amounts of nitrogenous wastes can also be eliminated through saliva too.

♦ **Disorders of excretory system:**

1. **Uremia :** It is presence of large amount of urea in blood due to malfunctioning of kidneys. It may lead to kidney failure.

   In such patients, urea is removed from blood by hemodialysis. In this, dialysing fluid has same composition as plasma except nitrogenous wastes. This makes a gradient and helps remove nitrogenous wastes from blood.

   Kidney transplantation is best possible method for treating acute kidney failure.
2. **Renal calculi :** In this, stone or insoluble mass of crystallized salts (oxalates etc.) is formed within kidney.
3. **Glomerulonephritis :** It is the inflammation of glomeruli of kidney. It leads to excretion of protein in urea, a condition called proteinuria.
4. **Glycosuria =** presence of glucose in urine.

   Ketonuria = presence of ketone bodies in urine.

♦ **Measurement of glomerular filtration rate :** Glomerular filtration rate (GFR) is the volume of fluid filtered from glomerular capillaries (i.e., blood) into the Bowman's capsule per unit time.

GFR is equal to the clearance rate when any solute is freely filtered and is neither reabsorbed nor secreted by the kidneys.

Creatinine is one such solute that is freely filtered, not reabsorbed and very small amount is secreted by peritubular capillaries. Therefore, GFR is calculated using creatinine clearance rate (C_{cr}).

$$C_{cr} = \frac{U_{cr} \times V}{P_{cr}}$$

Here, U_{cr} = creatinine concentration in urine sample.

V = urine flow rate.

P_{cr} = creatinine concentration in urine sample.

Example : A person has a plasma creatinine concentration of 0.01 mg/ml and in 1 hr produces 60 ml of urine with a creatinine concentration of 1.25 mg/ml. What is creatinine clearance rate and GFR.

$$C_{cr} = \frac{1.25\ \text{mg/ml} \times \frac{60\ \text{ml}}{60\ \text{min}}}{0.01\ \text{mg/ml}}$$

$$C_{cr} = \frac{1.25\ \text{mg/min}}{0.01\ \text{mg / ml}}$$

$$C_{cr} = 125\ \text{ml/min}$$

Because C_{cr} is a proxy measure of GFR, its value will be same i.e., 125 ml/min.

However, the method above is simple and less accurate. Medically relevant and more accurate C_{cr} can be calculated using various formulas. Cockcroft-Gault formula is one such formula.

Low values of P_{cr} show efficient kidney function and normal rate of blood flow to kidney.

High values of P_{cr} show deficient kidney filtration and less rate of blood flow to kidney.

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PRACTICE SET

SECTION - A : [Multiple Choice Questions (MCQ)]

1. ..... facilitates reabsorption of water by nephron
   (a) Loop of Henle (b) Medulla (c) Cortex (d) Pelvis

2. Brush border is found in
   (a) DCT (b) Bowman's capsule (c) PCT (d) Collecting duct

3. Ability of kidneys to produce concentrated urine is dependent upon .....
   (a) active transport (b) passive transport (c) diffusion (d) counter-current mechanism

4. Certain ions and molecules, for example, H^+ and penicilline are secreted from peritubular capillary network into
   (a) DCT (b) PCT (c) collecting duct (d) loop of Henle

5. Correct sequence of urine formation is
   (a) Filtration, reabsorption, secretion (b) Secretion, reabsorption, filtration
   (c) Reabsorption, secretion, filtration (d) Reabsorption, filtration, secretion

6. Creatinine is the end product of the metabolism of
   (a) ammonia (b) muscle (c) nucleotide (d) lipids

7. Glomerular capsule and convoluted tubule are always within .....
   (a) renal pelvis (b) renal medulla (c) renal cortex (d) both medulla and cortex

8. If a man takes large amount of protein, he is likely to excrete more amount of
   (a) glucose (b) urea and uric acid (c) water (d) salts

9. If a person undergoes a prolonged fasting then his urine will be found to contain higher levels of
   (a) ketones (b) amino acids (c) fats (d) glucose

10. Which of the following statements is correct with respect to kidney function regulation ?
    (a) During summer when body loses lot of water by evaporation, the release of ADH is suppressed.
    (b) When someone drinks lots of water, ADH release is suppressed.
    (c) Exposure to old temperature stimulates ADH release.
    (d) An increase in glomercular blood flow stimulates formation of angiotensin II.

SECTION - B : [Multiple Select Questions (MSQ)]

1. The following parts are found only in cortex of kidney
   (a) PCT (b) DCT (c) loop of Henle (d) collecting duct

2. Correct statement about counter-current mechanism are
   (a) osmolarity increases from cortex to medulla.
   (b) osmolarity decreases from cortex to medulla.
   (c) it involves nephrons only.
   (d) it involves nephrons and peritubular capillary network.

3. True statements for aldosterone hormone are
   (a) released in response to angiotensin-II signalling.
   (b) hyponatrimea enhances its release.
   (c) hyperkalemia enhances its release.
   (d) It acts mainly on principal cells in CD.

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ANSWER KEY

SECTION - A : [Multiple Choice Questions (MCQ)]

1. (a)	**2. (c)**	**3. (d)**	**4. (c)**	**5. (a)**
6. (b)	**7. (c)**	**8. (b)**	**9. (a)**	**10. (b)**

SECTION - B : [Multiple Select Questions (MSQ)]

1. (a, b)	**2. (a, d)**	**3. (a, b, c, d)**

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