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MBBS

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RENAL PHYSIOLOGY

1. ***Discuss the role of kidney in glucose homeostasis***

Along with the liver, the kidney has an important role in ensuring the energy needs during fasting periods. This organ has a vital role in absorbing the entire quantity of the filtered glucose. Having a glomerular filtration rate of 180 liters per day, it filters approximately 180 grams of glucose per day, bringing its contribution in maintaining normal fasting plasma glucose (FPG) levels. The reabsorption of glucose is ensured by the sodium-glucose cotransporter (SGLT) 2, responsible for the reabsorption of 90% of glucose, and SGLT1, that reabsorbs the remaining glucose.

 The primary function of kidneys is homeostasis. It is accomplished by the formation of urine. During the formation of urine, kidneys regulate various activities in the body, which are concerned with homeostasis such as:

Excretion of Waste Products

Kidneys excrete the unwanted waste products, which are formed during metabolic activities:

a. Urea (end product of amino acid metabolism)

b. Uric acid (end product of nucleic acid metabolism)

c. Creatinine (end product of metabolism in muscles)

d. Bilirubin (end product of hemoglobin degradation)

e. Products of metabolism of other substances.

Kidneys also excrete harmful foreign chemical substances such as toxins, drugs, heavy metals pesticides, etc.

1. ***Discuss the process of micturition.***

 Micturition or urination is the process of expelling urine from the bladder. This act is also known as voiding of the bladder. The excretory system in humans includes a pair of kidneys, two ureters, a urinary bladder and a urethra. The kidneys filter the urine and it is transported to the urinary bladder via the ureters where it is stored till its expulsion. The process of micturition is regulated by the nervous system and the muscles of the bladder and urethra. The urinary bladder can store around 350-400ml of urine before it expels it out.

Micturition is brought about by reflex contraction of a special muscle called the detrusor muscle after voluntary relaxation of the sphincter muscle.

Micturition is also known as voiding phase of bladder control and lasts for a short time. As the bladder becomes full, the stretch receptors increase their firing rate. This increases the urge to urinate and causes micturition reflex. It sometimes even causes involuntary urination.

*Human Urine*

On average, a normal adult excretes 1 to 1.5 L of urine per day. Normal human urine is a light yellow fluid majorly consisting of 95 per cent water and 5 per cent solid wastes. It is slightly acidic with a pH close to 6. Many endocrinal disorders can be diagnosed through urine analysis. For example, if a patient has diabetes, the presence of glucose and ketone bodies in the urine can help detect the disease. Thus it is a major clinical diagnostic element.

***Stages of Micturition***

The urinary bladder has two distinct stages or phases:

A Resting or filling stage

B Voiding stage

1. **Resting or Filling Stage:** It is in this phase of the bladder that the urine is transported from the kidneys via the ureters into the bladder. The ureters are thin muscular tubes that arise from each of the kidneys and extend downwards where they enter the bladder obliquely. The oblique placement of the ureters in the bladder wall serves a very important function. The opening of the ureter into the urinary bladder is not guarded by any sphincter or muscle. Therefore, this oblique nature of opening prevents the urine from re-entering the ureters. At the same time, the main muscle of the urinary bladder, the detrusor muscle, is relaxing allowing the bladder to distend and accommodate more urine.
2. **Voiding Stage:** During this stage, both the urinary bladder and the urethra come into play together. The detrusor muscle of the urinary bladder which was relaxing so far starts to contract once the bladder’s storage capacity is reached. The urethra is controlled by two sets of muscles: The internal and external urethral sphincters. The internal sphincter is a smooth muscle whereas the external one is skeletal. Both these sphincters are in a contracted state during the filling stage. When the bladder is filled with urine, the nerves in it are triggered, which in turn stimulates the need to urinate. The brain signals urinary bladder to contract. The receptors of the urinary bladder send a signal to the central nervous system, in response to which the nervous system sends a signal that incites the contraction of the urinary bladder. Through the urinary opening at the urethra, the urine is eliminated, and the process is called micturition. The neural mechanism involved is called the micturition reflex.

**Problems Associated With Micturition**

There are several factors which affect the process of micturition. Some of these can be due to physical trauma or disease; others are psychological in nature. The following are a few disorders that affect micturition:

.Detrusor Instability – This is a condition where the detrusor muscle contracts without any apparent reason. This muscle is responsible for contracting the bladder and help with the micturition process. As a result, detrusor instability results in urinary incontinence.

.Urinary Retention – This condition is characterized by the inability to empty the bladder completely. The onset may be gradual or sudden. The causes can range from a blockage in the urethra, nerve problems and weak bladder muscles.

.Spinal Cord Trauma – Injuries to the spinal cord, specifically the tenth thoracic vertebra (T10) can cause the bladder to be overactive or cause urinary incontinence.

1. ***Explain the juxtaglomerular apparatus.***

The juxtaglomerular apparatus (also known as the juxtaglomerular complex) is a structure in the kidney that regulates the function of each nephron, the functional units of the kidney. The juxtaglomerular apparatus is named because it is next to the glomerulus.

The juxtaglomerular apparatus is part of the kidney nephron, next to the glomerulus. It is found between afferent arteriole and the distal convoluted tubule of the same nephron. This location is critical to its function in regulating renal blood flow and glomerular filtration rate.

The juxtaglomerular apparatus is a specialized structure formed by the distal convoluted tubule and the glomerular afferent arteriole. It is located near the vascular pole of the glomerulus and its main function is to regulate blood pressure and the filtration rate of the glomerulus. The macula densa is a collection of specialized epithelial cells in the distal convoluted tubule that detect sodium concentration of the fluid in the tubule. In response to elevated sodium, the macula densa cells trigger contraction of the afferent arteriole, reducing flow of blood to the glomerulus and the glomerular filtration rate. The juxtaglomerular cells, derived from smooth muscle cells, of the afferent arteriole secrete renin when blood pressure in the arteriole falls. Renin increases blood pressure via the renin-angiotensin-aldosterone system. Lacis cells, also called extraglomerular mesangial cells, are flat and elongated cells located near the macula densa.

**Function**

**Juxtaglomerular cells:** Renin is produced by juxtaglomerular cells. These cells are similar to epithelium and are located in the tunica media of the afferent arterioles as they enter the glomeruli. The juxtaglomerular cells secrete renin in response to:

.Stimulation of the beta-1 adrenergic receptor

.Decrease in renal perfusion pressure (detected directly by the granular cells)

.Decrease in NaCl concentration at the macula densa, often due to a decrease in glomerular filtration rate

**Extraglomerular mesangial cells**

Extraglomerular mesangial cells are located in the junction between the afferent and efferent arterioles. These cells have a contractile property similar to vascular smooth muscles and thus play a role in “regulating Glomerular Filtration Rate” by altering the vessel diameter. Renin is also found in these cells.

**Macula densa**

At the point where the afferent arterioles enter the glomerulus and the efferent arteriole leaves it, the tubule of the nephron touches the arterioles of the glomerulus from which it rose. At this location, in the wall of the distal convoluted tubule, there is a modified region of tubular epithelium called the macula densa. Cells in the macula densa respond to changes in the sodium chloride levels in the distal tubule of the nephron via the tubuloglomerular feedback (TGF) loop. The macula densa's detection of elevated sodium chloride, which leads to an increase in Glomerular Filtration Rate, is based on the concept of purinergic signaling. An increase in the salt concentration causes several cell signals to eventually cause the adjacent afferent arteriole to constrict. This decreases the amount of blood coming from the afferent arterioles to the glomerular capillaries, and therefore decreases the amount of fluid that goes from the glomerular capillaries into the Bowman's space (the glomerular filtration rate). When there is a decrease in the sodium concentration, less sodium is reabsorbed in the macula densa cells. The cells increase the production of nitric oxide and Prostaglandins to vasodilate the afferent arterioles and increase renin release.

**Clinical significance**

Excess secretion of renin by the juxtaglomerular cells can lead to excess activity of the renin–angiotensin system, hypertension and an increase in blood volume. This is not responsive to the usual treatment for essential hypertension, namely medications and lifestyle modification. One cause of this can be increased renin production due to narrowing of the renal artery, or a tumour of juxtaglomerular cells that produces renin. These will lead to secondary hyperaldosteronism, which will cause hypertension, high blood sodium, low blood potassium, and metabolic alkalosis.

1. ***Discuss the role of kidney in regulation of blood pressure.***

Kidneys play an important role in the long-term regulation of arterial blood pressure by two ways:

1. By regulating the volume of extracellular fluid
2. Through renin-angiotensin mechanism.

*REGULATION OF BLOOD PRESSURE –LONG-TERM REGULATION*

When blood pressure alters slowly in several days/months/years, the nervous mechanism adapts to the altered pressure and loses the sensitivity for the changes. It cannot regulate the pressure any more. In such conditions, the renal mechanism operates efficiently to regulate the blood pressure. Therefore, it is called long term regulation.

 Kidneys regulate arterial blood pressure by two ways:

1. by regulation of ECF volume

2. through renin-angiotensin mechanism.

 *BY REGULATION OF EXTRACELLULAR FLUID VOLUME*

When the blood pressure increases, kidneys excrete large amounts of water and salt, particularly sodium, by means of pressure diuresis and pressure natriuresis.

Pressure diuresis is the excretion of large quantity of water in urine because of increased blood pressure.

Even a slight increase in blood pressure doubles the water excretion. Pressure natriuresis is the excretion of large quantity of sodium in urine.

Because of diuresis and natriuresis, there is a decrease in ECF volume and blood volume, which in turn brings the arterial blood pressure back to normal level.

When blood pressure decreases, the reabsorption of water from renal tubules is increased. This in turn, increases ECF volume, blood volume and cardiac output, resulting in restoration of blood pressure.

 *THROUGH RENIN-ANGIOTENSIN MECHANISM*

*Actions of Angiotensin II*

When blood pressure and ECF volume decrease, renin secretion from kidneys is increased. It converts angiotensinogen into angiotensin I. This is converted into angiotensin II by ACE (angiotensin converting enzyme).

Angiotensin II acts in two ways to restore the blood pressure:

i. It causes constriction of arterioles in the body so that the peripheral resistance is increased and blood pressure rises. In addition, angiotensin II causes constriction of afferent arterioles in kidneys, so that glomerular filtration reduces.

This results in retention of water and salts, increases ECF volume to normal level. This in turn increases the blood pressure to normal level.

ii. Simultaneously, angiotensin II stimulates the adrenal cortex to secrete aldosterone. This hormone increases reabsorption of sodium from renal tubules. Sodium reabsorption is followed by water reabsorption, resulting in increased ECF volume and blood volume. It increases the blood pressure to normal level.

*Actions of Angiotensin III and Angiotensin IV*

Like angiotensin II, the angiotensins III and IV also increase the blood pressure and stimulate adrenal cortex to secrete aldosterone.

1. ***Discuss the role of the kidney in calcium homeostasis.***

Kidneys play a role in the regulation of blood calcium level by activating 1, 25-dihydroxycholecalciferol into vitamin D. Vitamin D is necessary for the absorption of calcium from intestine. Under normal blood calcium concentrations, almost all of the calcium that enters glomerular filtrate is reabsorbed from the tubular system back into blood, which preserves blood calcium levels. If tubular reabsorption of calcium decreases, calcium is lost by excretion into urine.

 Parathormone (PTH) increases the reabsorption of calcium from the renal tubules along with magnesium ions and hydrogen ions. It increases calcium reabsorption mainly from distal convoluted tubule and proximal part of collecting duct. PTH also increases the formation of 1, 25-dihydroxycholecalciferol (activated form of vitamin D) from 25-hydroxycholecalciferol in kidneys.

Parathyroid hormone serves to increase blood concentrations of calcium. Mechanistically, parathyroid hormone preserves blood calcium by several major effects: .It stimulates production of the biologically-active form of vitamin D within the kidney.

.It facilitates mobilization of calcium and phosphate from bone. To prevent detrimental increases in phosphate, parathyroid hormone also has a potent effect on the kidney to eliminate phosphate (phosphaturic effect).

.It maximizes tubular reabsorption of calcium within the kidney. This activity results in minimal losses of calcium in urine.

Vitamin D acts also to increase blood concentrations of calcium. It is generated through the activity of parathyroid hormone within the kidney. Far and away the most important effect of vitamin D is to facilitate absorption of calcium from the small intestine. In concert with parathyroid hormone, vitamin D also enhances fluxes of calcium out of bone.

Calcitonin is a hormone that functions to reduce blood calcium levels. It is secreted in response to hypercalcemia and has at least two effects:

.It enhances excretion of calcium into urine.

.It inhibits bone resorption, which would minimize fluxes of calcium from bone into blood.

Although calcitonin has significant calcium-lowing effects in some species, it appears to have a minimal influence on blood calcium levels in humans.