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**Course Title:** Renal Physiology Body Fluid and Temperature Regulation.

**Course Code:** PHS 303.

**Questions:**

1. Discuss the role of kidney in glucose homeostasis.
2. Discuss the process of micturition.
3. Explain juxtaglomerular apparatus.
4. Discuss the role of kidney in regulation of blood pressure.
5. Discuss the role of kidney in calcium homeostasis.

**Question 1:**

The kidneys are involved in maintaining glucose homeostasis through two different mechanisms: gluconeogenesis and reabsorption into the general circulation of glucose from glomerular filtrate in order to preserve energy.

1. **Renal Gluconeogenesis:**

In the kidney, the renal medulla is characterized mainly by glucose utilization and the renal cortex is responsible for glucose release. The renal cortex contains gluconeogenic enzymes and it can synthesize glucose-6-phosphate from precursors (lactate, glutamine, glycerol and alanine). Because it contains glucose-6-phosphate, it is able to produce and release glucose into the circulation. The kidneys produce between 2.0-2.5µmol of glucose/kg/min thereby contributing about 20-25% of circulating glucose.

Renal gluconeogenesis can increase by approximately twofold and can represent approximately 60% of endogenous glucose production in the postprandial state. Gluconeogenesis in the kidneys exceeds renal glucose consumption. It is important in the prevention of hypoglycemia, and its inappropriate increase in diabetic patients contributes to the development of hyperglycemia.

1. **Glucose Reabsorption:**

In normal conditions, the kidneys can reabsorb as much glucose as possible, the result being a virtually glucose free urine. Approximately 180g of glucose are filtered by the glomeruli from plasma, daily but all of this quantity is reabsorbed through glucose transporters that are present in the cell membranes located in the proximal tubules. These glucose transporters have a limited capacity of reabsorption. If this capacity is exceeded, glucose usually appears in the urine.

The glucose transporters expressed in the renal proximal tubule ensure that less than 0.5g/day (range: 0.03-0.3g/day) is excreted in the urine of healthy adults. More water than glucose is reabsorbed resulting in an increase in the glucose concentration in the urine along the tubule. Consequently, the affinity of the transporters for glucose along the tubule increases to allow for complete reabsorption of glucose from the urine.

**Question 2:**

**Micturition**

Micturition is the process of expelling urine from the body. 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 muscles involved are:

* The detrusor muscle – smooth muscle of the bladder wall.
* The internal and external sphincters of the urethra.

The internal sphincter and the detrusor muscle are both under autonomic control while the external sphincter is a voluntary muscle under the control of voluntary nerves. The bladder normally accommodates up to 300-400ml in adults. When the bladder is distended, it sends signals to the brain, which is perceived as the “full bladder” sensation. The process of emptying the urine into the urethra is regulated by nervous signals, both from the somatic and the autonomic nervous system. The autonomic nervous system comprises of both the sympathetic and the parasympathetic nervous system.

**Process of Micturition:**

The micturition process consists of two phases:

1. Storage/Resting/Filling phase
2. Voiding phase
3. **Resting/Storage/Filling Phase:**

It is in this phase that the urine is transported from the kidneys via the ureters into the bladder. The ureters are thin muscular tubes that arise from each kidney 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 detrusor muscle of the bladder is relaxing, allowing the bladder to distend and accommodate more urine. The urinary bladder in a healthy urinary system can store up to 16 ounces of urine for 2-5 hours easily.

1. **Voiding Phase:**

When the storage capacity of the bladder is reached, the nerves in it are triggered, which in turn stimulates the need to urinate. The brain signals the 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 expelled. This process is called **Micturition** and the neural mechanism involved is known as the **Micturition Reflex**.

The micturition reflex is ultimately generated in the spinal cord after it receives reflexes from the pontine region in the brain. Once the bladder and urethra receive the signals to empty the bladder, the two sphincters relax and the detrusor muscle causes the contractions of the bladder. Along with these muscles, the muscles of the abdomen also play a role by putting pressure on the bladder wall. This leads to complete emptying of the bladder.

**Question 3:**

The juxtaglomerular apparatus (JGA), 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 JGA is part of the kidney nephron, located next to the glomerulus. It is a specialized structure formed by the distal convoluted tubule (DCT) and the glomerular afferent arteriole. It is located near the vascular pole of the glomerulus and its main function is to regulate renal blood flow and the filtration rate of the glomerulus.

The juxtaglomerular apparatus consists of three types of cells:

1. Juxtaglomerular cells
2. Macula densa
3. Extraglomerular mesangial cells
4. **Juxtaglomerular Cells:**

The juxtaglomerular cells (also known as **Granular cells**) are derived from smooth muscle 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 synthesize and store renin which is secreted in response to:

* Stimulation of the beta-1 adrenergic receptor.
* Decrease in renal perfusion pressure.
* Decrease in NaCl concentration at the macula densa, often due to a decrease in glomerular filtration rate.

The juxtaglomerular cells could be considered the “effector arm” of the renin-angiotensin-aldosterone axis.

1. **Macula Densa:**

The macula densa is a collection of specialized epithelial cells in the distal convoluted tubule that detect sodium chloride concentration of the fluid in the tubule via the tubuloglomerular feedback (TGF) loop. The macula densa can be considered the “sensory arm” of the renin-angiotensin-aldosterone axis. Elevated sodium chloride levels leads to an increase in glomerular filtrate rate (GFR).

An increase in NaCl 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, that is the GFR.

When there is a decrease in NaCl concentration, less sodium is reabsorbed in the macular densa cells. The cells increase the production of nitric oxide and prostaglandins to vasodilate the afferent arterioles and increase renin release.

1. **Extraglomerular Mesangial Cells:**

These cells are also called **Lacis cells**. They are flat and elongated cells located near the macula densa, 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 (GFR) by altering the vessel diameter. Renin is also found in these cells.

**Question 4:**

The kidneys play a central role in the regulation of arterial blood pressure. A large body of experimental and physiological evidence indicates that renal control of extracellular volume and renal perfusion pressure are closely involved in maintaining the arterial circulation and blood pressure. Renal artery perfusion pressure directly regulates sodium excretion; a process known as pressure natriuresis, and influences the activity of various vasoactive systems such as the renin–angiotensin–aldosterone (RAS) system. Along with vessel morphology, blood viscosity is one of the key factors influencing resistance and hence blood pressure. A key modulator of blood viscosity is the renin-angiotensin system (RAS) or the renin-angiotensin-aldosterone system (RAAS), a hormone system that regulates blood pressure and water balance.

The blood pressure in the body depends upon:

* The force by which the heart pumps out blood from the ventricles of the heart - and this is dependent on how much the heart muscle gets stretched by the inflowing blood into the ventricles.
* The degree to which the arteries and arterioles constrict-- increases the resistance to blood flow, thus requiring a higher blood pressure.
* The volume of blood circulating round the body; if the volume is high, the ventricles get more filled, and the heart muscle gets more stretched.

The kidney influences blood pressure by:

* Causing the arteries and veins to constrict
* Increasing the circulating blood volume

Specialized cells called macula densa are located in a portion of the distal tubule located near and in the wall of the afferent arteriole. These cells sense the Na in the filtrate, while the arterial cells (juxtaglomerular cells) sense the blood pressure. When the blood pressure drops, the amount of filtered Na also drops. The arterial cells sense the drop in blood pressure, and the decrease in Na concentration is relayed to them by the macula densa cells. The juxtaglomerular cells then release an enzyme called renin.

Renin converts angiotensinogen (a peptide, or amino acid derivative) into angiotensin-1. Angiotensin-1 is thereafter converted to angiotensin-2 by an angiotensin-converting enzyme (ACE), found in the lungs. Angiotensin-2 causes blood vessels to contract -- the increased blood vessel constrictions elevate the blood pressure. When the volume of blood is low, arterial cells in the kidneys secrete renin directly into circulation. Plasma renin then carries out the conversion of angiotensinogen released by the liver to angiotensin-1. Angiotensin-1 is subsequently converted to angiotensin-2 by the enzyme angiotensin converting enzyme found in the lungs. Angiotensin-2m a potent vasoactive peptide causes blood vessels to constrict, resulting in increased blood pressure. Angiotensin-2 also stimulates the secretion of the hormone aldosterone from the adrenal cortex.

Aldosterone causes the tubules of the kidneys to increase the reabsorption of sodium and water into the blood. This increases the volume of fluid in the body, which also increases blood pressure. If the renin-angiotensin-aldosterone system is too active, blood pressure will be too high. Many drugs interrupt different steps in this system to lower blood pressure. These drugs are one of the main ways to control high blood pressure (hypertension), heart failure, kidney failure, and harmful effects of diabetes. It is believed that angiotensin-1 may have some minor activity, but angiotensin-2 is the major bioactive product. Angiotensin-2 has a variety of effects on the body: throughout the body, it is a potent vasoconstrictor of arterioles.

**Question 5:**

About 50% of plasma calcium (ionized and complexed form; ultra-filterable fraction, excluding the protein bound form) is freely filtered through the renal glomerulus, and 99% of the filtered calcium is actually reabsorbed along renal tubules. The excreted calcium in the final urine is about 200 mg per day in an adult person with an average diet. Several factors are involved in the regulation of calcium in renal tubules. PTH and activated vitamin D enhance calcium reabsorption in the thick ascending limb (TAL), distal convoluted tubule (DCT) and/or connecting tubule (CNT), and estrogen promotes calcium absorption in the DCT/CNT.

Acidosis contributes to hypercalciuria by reducing calcium reabsorption in the proximal tubule (PT) and DCT, and alkalosis vice versa. Diuretics like thiazide and furosemide also alter calcium absorption in the renal tubules; thiazide promotes calcium reabsorption and furosemide inhibits it. Plasma calcium itself also controls renal calcium absorption through altered PTH secretion as well as via binding to the calcium sensing receptor (CaSR) in the TAL.

To facilitate Ca2+ reabsorption along renal tubules:

1. voltage difference between the lumen and blood compartment should be favorable for Ca2+ passage, i.e., a positive voltage in the lumen.
2. concentration difference should be favorable for Ca2+ passage with a higher Ca2+ concentration in the lumen.
3. an active transporter should exist if the voltage or concentration difference is not favorable for Ca2+ reabsorption.

Each renal tubular segment has a different Ca2+ concentration difference or voltage environment for its unique mechanism for calcium reabsorption.

Fifty to sixty percent of filtered calcium is absorbed in parallel with sodium and water in the PT, suggesting that the passive pathway is the main route of Ca2+ absorption in this segment. Claudin-2 is especially concentrated in the tight junction and also expressed in the basolateral membrane of the PT as the candidate for paracellular Ca2+ channel in the PT. There is no evidence that Ca2+ reabsorption occurs in the thin descending and ascending limb.

In the TAL, 15% of filtered calcium is absorbed, and the passive absorption through paracellular space is known as the main mechanism. Paracellin-1 (claudin-16) is exclusively expressed in the tight junction of TAL and has been known as the important magnesium channel in the TAL. Paracellin-1 mutation caused hypercalciuria and nephrocalcinosis in addition to hypomagnesemia. This finding supports that paracellin-1 is not only the main Mg2+ channel, but also works as the paracellular Ca2+ channel in the TAL.

There are some evidences that active transport occurs in the TAL, but no specific channel has yet been identified. The CaSR is a member of G protein-coupled receptors and suppresses PTH secretion by sensing high plasma Ca2+ level in the parathyroid glands. In the kidney, the CaSR is most highly expressed in the TAL. Familial hypocalciuric hypercalcemia (FHH) is an autosomal dominant disease due to the mutation of CaSR gene, and is manifested as hypercalcemia, hypophosphatemia, parathyroid hyperplasia, and unusually low renal clearance of calcium. Hypocalciuria, despite of hyperactivity of PTH in FHH, suggests that CaSR plays a direct role in Ca2+ absorption, especially in the TAL independent to PTH action.

Although only 10-15% of filtered Ca2+ is absorbed in the DCT and CNT, these are the main sites in which the fine regulation of Ca2+ excretion and the major action of PTH and activated vitamin D occur. In the DCT and CNT, the luminal voltage is negative and Ca2+ concentration in the lumen is lower than that of plasma. Thus, active transport mechanism against voltage and concentration gradient should exist in these segments. Several Ca2+ transporting proteins are involved in this active transmembrane transport of Ca2+ in the DCT and CNT.

Transcellular Ca2+ reabsorption can occur by three steps:

1. entry of Ca2+ through the calcium channels (TRPV5, TRPV6) in the apical membrane.
2. binding of Ca2+ with calcium binding protein (calbindin) and diffusion in the cytoplasm (which enables no significant change in the intracellular ionized calcium(iCa2+).
3. Ca2+ extrusion via an ATP-dependent plasma membrane Ca2+-ATPase (PMCA1b) and an Na2+/Ca2+ exchanger (NCX1) in the basolateral membrane.

In the collecting duct (CD), there is no evidence that Ca2+ reabsorption occurs even though calcium channel (TRPV6) was documented to be expressed in CD cells. Each renal tubule has a unique environment and plays a different role in Ca2+ reabsorption. The coordinated play of different renal tubules could maintain harmony of renal Ca2+ handling.