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17/MHS01/134

PHYSIOLOGY

RENAL PHYSIOLOGY (BODY FLIUD AND TEMPERATURE REGULATION)

300 LEVEL

MEDICINE AND SURGERY

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.

ANSWERS

1. **Kidney is important in glucose homeostasis.**

The kidney has an important role in ensuring the energy needs during fasting periods are met. 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

1. Renal glucogenesis: From the point of view of glucose utilization, the kidney is considered as 2 separate organs; the renal medulla is characterized mainly by glucose utilization and the renal cortex is responsible for glucose release. The separation of these activities represents the consequence of differences in the distribution of numerous enzymes along the nephron. The cells in the renal medulla can use only glucose for their needs (like the brain) and they have enzymes capable of glucose-phosphorylation and glycolysis. They can therefore phosphorylate important amounts of glucose and accumulate glycogen but, because these cells do not have glucose-6-phosphatase or any other gluconeogenic enzymes, they are unable to release glucose into the bloodstream. Moreover, the cells in the renal cortex have gluconeogenic enzymes and they can produce and release glucose into the circulation. However these cells cannot synthesize glycogen because they have little phosphorylating capacity. Micturition is a process where urine is expelled from the body from the urinary bladder through the urethra. Animals and humans have a specialized system of organs known as the excretory system to eliminate the waste products from the body. It is brought about by reflex contraction of a special muscle called the detrusor muscle after voluntary relaxation of the sphincter muscle. Urine is collected in the nephrons and flows into the ureters. The human excretory system consists of a pair of kidneys and ureters, a urinary bladder, and a urethra. The kidneys play a major role in the process of urine formation and its excretion. The urine formed is stored in the urinary bladder. Therefore, after an overnight fast, the liver produces 75–80% of glucose released into the circulation and the remaining 20–25% is derived from the kidneys. Lactate represents the predominant gluconeogenic precursor in both organs, but regarding the amino acids, the kidney prefers to use glutamine, whereas the liver preferentially uses alanine. Insulin can suppress glucose release in both organs with almost comparable efficacy, whereas glucagon stimulates hepatic glucose release only.
2. Glucogenolysis: Glycogenolysis is the breakdown of glycogen to glucose-6-phosphate and a hydrolysis reaction (using glucose-6-phosphatase) in order to free glucose. The liver is the only organ that contains glucose-6-phosphatase. So, the cleavage of hepatic glycogen releases glucose, while the cleavage of glycogen from other sources can release only lactate. Lactate, that is generated via glycolysis, is often absorbed by other organs and helps regenerating glucose
3. Glucose reabsorbtion: Apart from the important role in gluconeogenesis and the role of renal cortex in glucose uptake, the kidneys contribute to glucose homeostasis by filtering and reabsorbing glucose. In normal conditions, the kidneys can reabsorb as much glucose as possible, the result being a virtually glucose free urine. Approximately 180 grams of glucose are filtered by the glomeruli from plasma, daily but all of this quantity is reabsorbed through glucose transporters that are present in cell membranes located in the proximal tubules.
4. **Micturition**

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.

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.

There are 2 stages of micturition

1. Storage phase: The urinary bladder is a balloon-shaped, hollow, muscular, organ that acts as the storage organ for urine. The urinary bladder in a healthy urinary system can store up to 16 ounces of urine for 2 to 5 hours easily. The circular sphincter muscles prevent leakage of urine. They close tightly around the opening of the bladder into the tube (urethra) that allows the passage of urine outside the body.
2. Voiding Phase: 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.

1. **The juxtaglomerular apparatus**

The juxtaglomerular apparatus (JGA) is located between the afferent arteriole and the returning distal convoluted tubule of the same nephron. It is responsible for regulating both intrarenal (tubuloglomerular feedback) and extrarenal (renin-angiotensin-aldosterone) mechanisms necessary to maintain both renal and entire body volume status.

The three components of the JGA are the following:

1. The juxtaglomerular cells of the afferent arteriole: synthesize and store renin, which is secreted in response to specific stimuli (e.g., low blood flow, decreased NaCl delivery). The juxtaglomerular cells could be considered the “effector arm” of the renin-angiotensin-aldosterone axis.
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3. Mesangial cells, which form connections via actin and microtubules which allow for selective vasoconstriction/vasodilation of the renal afferent and efferent arterioles with mesangial cell contraction.
4. **The kidneys and their influence on blood pressure**

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 The kidneys play a central role in the regulation of arterial blood pressure. A large body of experimental 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:

1. 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.
2. The degree to which the arteries and arterioles constrict increases the resistance to blood flow, thus requiring a higher blood pressure.
3. 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:

1. Causing the arteries and veins to constrict.
2. 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.

1. **Endocrine Control of Calcium and Phosphate Homeostasis**

It would be very difficult to name a physiologic process that does not depend, in one way or another, on calcium. It is critical to maintain blood calcium concentrations within a tight normal range. Deviations above or below the normal range frequently lead to serious disease.

1. Hypocalcemia refers to low blood calcium concentration. Clinical signs of this disorder reflect increased neuromuscular excitability and include muscle spasms, tetany and cardiac dysfunction.
2. Hypercalcemia indicates a concentration of blood calcium higher than normal. The normal concentration of calcium and phosphate in blood and extracellular fluid is near the saturation point; elevations can lead to diffuse precipitation of calcium phosphate in tissues, leading to widespread organ dysfunction and damage.

Preventing hypercalcemia and hypocalcemia is largely the result of robust endocrine control systems.

There are three major pools of calcium in the body:

1. Intracellular calcium: A large majority of calcium within cells is sequestered in mitochondria and endoplasmic reticulum. Intracellular free calcium concentrations fluctuate greatly, from roughly 100 nM to greater than 1 uM, due to release from cellular stores or influx from extracellular fluid. These fluctuations are integral to calcium's role in intracellular signaling, enzyme activation and muscle contractions.
2. Calcium in blood and extracellular fluid: Roughly half of the calcium in blood is bound to proteins. The concentration of ionized calcium in this compartment is normally almost invariant at approximately 1 mM, or 10,000 times the basal concentration of free calcium within cells. Also, the concentration of phosphorus in blood is essentially identical to that of calcium.
3. Bone calcium: A vast majority of body calcium is in bone. Within bone, 99% of the calcium is tied up in the mineral phase, but the remaining 1% is in a pool that can rapidly exchange with extracellular calcium.

As with calcium, the majority of body phosphate (approximately 85%) is present in the mineral phase of bone. The remainder of body phosphate is present in a variety of inorganic and organic compounds distributed within both intracellular and extracellular compartments. Normal blood concentrations of phosphate are very similar to calcium.

Fluxes of Calcium and Phosphate

Maintaining constant concentrations of calcium in blood requires frequent adjustments, which can be described as fluxes of calcium between blood and other body compartments. Three organs participate in supplying calcium to blood and removing it from blood when necessary:

The small intestine is the site where dietary calcium is absorbed. Importantly, efficient absorption of calcium in the small intestine is dependent on expression of a calcium-binding protein in epithelial cells.

Bone serves as a vast reservoir of calcium. Stimulating net resorption of bone mineral releases calcium and phosphate into blood, and suppressing this effect allows calcium to be deposited in bone.

The kidney is critically important in calcium homeostasis. 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.

Hormonal Control Systems

Maintaining normal blood calcium and phosphorus concentrations is managed through the concerted action of three hormones that control fluxes of calcium in and out of blood and extracellular fluid:

Parathyroid hormone serves to increase blood concentrations of calcium. Mechanistically, parathyroid hormone preserves blood calcium by several major effects:

1. Stimulates production of the biologically-active form of vitamin D within the kidney.
2. 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).
3. Maximizes tubular reabsorption of calcium within the kidney. This activity results in minimal losses of calcium in urine.
4. 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:

1. Suppression of renal tubular reabsorption of calcium. In other words, calcitonin enhances excretion of calcium into urine.
2. Inhibition of bone reabsorption, 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.