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**RENAL PHYSIOLOGY ASSIGNMENT**

**300L**

QUESTONS:

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. **The Role of Kidney in Glucose Homeostasis**

It is only in recent years that the attention was drawn on the important role of the kidney in glucose homeostasis. Nevertheless, 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 co-transporter (SGLT) 2, responsible for the reabsorption of 90% of glucose, and SGLT1, that reabsorbs the remaining glucose.

Despite the large amount of data regarding the implication of the kidneys in glucose homeostasis, this organ is often overlooked as a key player in glucose metabolism. But the awareness of the renal mechanisms of glucose control is likely to increase due to the development of new types of glucose-lowering drugs that target this metabolic pathway.

The plasma glucose concentration is determined by the amount of glucose synthesized, and the one removed from the circulation and metabolized. This concentration must be maintained within a relatively narrow range despite the wide daily fluctuations in glucose ingestion and glucose demands in various tissues. Other substrates such as free fatty acids (FFAs), glycerol, lactate and ketone bodies have greater daily fluctuations. This can be explained by the need of the body to protect himself against hyper- and hypoglycemia. Hyperglycemia is associated with both chronic effects (such as nephropathy, retinopathy, neuropathy and premature atherosclerosis) and also acute complications (including diabetic ketoacidosis and hyperosmolar hyperglycemic state that are associated with higher morbidity and mortality). Hypoglycemia is also harmful because it can cause neurological events (including coma, seizures), cardiac arrhythmias and death.

The regulation of endogenous production of glucose is determined by hormonal and neural factors. In the acute phase, glucoregulatory mechanisms involve insulin, glucagon and catecholamines and they can effect changes in plasma glucose levels in a matter of minutes. Insulin is able to suppress glucose release in both the kidney and liver by direct enzyme activation ⁄ deactivation and by reducing the availability of gluconeogenic substrates. Glucagon has no effect on the kidneys, but it stimulates glycogenolysis and gluconeogenesis in the liver. Catecholamines also have multiple acute actions. They can stimulate renal glucose release and glucagon secretion and inhibit insulin secretion.

The kidneys are involved in maintaining glucose homeostasis through three different mechanisms: gluconeogenesis; glucose uptake from the blood for its own energy requests and reabsorption into the general circulation of glucose from glomerular filtrate in order to preserve energy.

* Renal gluconeogenesis: 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. After a 16-h overnight fast, approximately 10 µmol ⁄ (kg /min) of glucose is released into the circulation. Almost 50% of this is the result of glycogenolysis from the liver stocks and the other half is produced by liver and kidney gluconeogenesis. The renal cortex (like the liver) contains gluconeogenic enzymes and it can synthesize glucose-6-phosphate from precursors (lactate, glutamine, glycerol and alanine). Because it contains glucose-6-phosphatase, it is able to release glucose into the blood stream and the human liver and kidneys are the only organs that can perform gluconeogenesis. 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. Several studies have indicated that human kidneys and liver provide approximately the same amounts of glucose through gluconeogenesis in post absorptive period. If the duration of fasting is increased, the glycogen stores are depleted and gluconeogenesis produces all the glucose released into circulation. An important aspect is that kidney and liver use different gluconeogenic precursors and several hormones have different effects on their release of glucose. 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. Catecholamines normally have a direct effect only on renal glucose release, but their effect on both hepatic and renal glucose release may be indirect by increasing the quantity of gluconeogenic substrates available and by suppressing insulin secretion. Other hormones, such as growth hormone, cortisol and thyroid hormones can stimulate hepatic glucose release over a great period of time. Their effects on the kidneys regarding glucose release in humans are not completely deciphered. In the postprandial state the situation changes significantly. Postprandial glucose levels in the plasma are determined by insulin and glucagon levels. After glucose ingestion, plasma glucose levels reach the peak in 60–90 minutes and they return to post-absorptive levels in almost 3–4 h. The plasma insulin increases four times and the plasma glucagon levels decrease by 50%. Meyer et al. indicated that endogenous glucose release is reduced by almost 60% and hepatic glycogenolysis drops to zero in the 4- to 6-h period after meal ingestion .This is happening because this period determines the refilling of hepatic glycogen stores and inhibition of endogenous glucose release is able to limit postprandial hyperglycemia. There is also a reduction in hepatic gluconeogenesis by 82% and glucose molecules generated through hepatic gluconeogenesis are also directed into hepatic glycogen, not only released in the circulation.
* Glycogenolysis: 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.
* Glucose Reabsorption: 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. These glucose transporters have a limited capacity of reabsorption. If this capacity is exceeded, glucose usually appears in the urine. The tubular maximum for glucose (TmG), the term used for the maximum capacity, can vary from 260 to 350 mg/min/1.73 m2 in healthy subjects. It corresponds to blood glucose levels of 180-200 mg/dL. When the blood glucose is very high and the TmG is reached, the transporters cannot reabsorb all the glucose and glucosuria occurs. Nevertheless, there can be slight differences between the nephrons and the inaccurate nature of biological systems may potentially lead to the development of glucosuria when blood glucose is below TmG. Glucosuria may occur at lower plasma glucose levels in certain conditions of hyper filtration (e.g. pregnancy), but as a consequence of hyper filtration and not of significant hyperglycemia. In a given day, the kidneys can produce, via gluconeogenesis, 15–55g glucose and it can metabolize 25–35g glucose. Regarding the glucose metabolic pathways, it is obvious that renal reabsorption represents the main mechanism by which the kidney is involved in glucose homeostasis. Therefore, the change in tubular glucose reabsorption may have a considerable impact on glucose homeostasis.

1. **Process of Micturition:**  micturition is the process of expelling urine from the bladder. This act is also known as voiding of the bladder. The excretory system of the body 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.

Stages of Micturition: the urinary bladder has two distinct stages which are; the resting or filling stage and the voiding stage.

* 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 the 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.
* 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 stge.

Micturition Reflex: the micturition reflex is ultimately generated from the level of the spinal cord after it receives reflexes from the pontine region in the brain. Once the bladder and the urethra receive the signals to empty the bladder, the two sphincters relax and the detrusor muscle causes the contractors 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.

1. **Juxtaglomerular Apparatus**: this is a specialised organ situated near the glomerulus of each nephron. It is formed by three different structures; the macula densa, extraglomerular mesangial cells and the juxtaglomerular cells.

* The macula densa: this is the end portion of thick ascending segment before it opens into distal convoluted tubule.it is formed by tightly packed cuboidal epithelial cells. Macula densa is situated between afferent and efferent arterioles of the same nephron.
* Extraglomerular mesangial cells: these are situated in the triangular region bound by afferent arteriole, efferent arteriole and macula densa. Besides extraglomerular mesangial cells there is another type of mesangial cells situated in between glomerular capillaries called glomerular mesangial. The glomerular mesangial cells support the glomerular capillary loops by surrounding the capillaries in the form of a cellular network.
* The juxtaglomerular cells: these are specialised smooth muscle cells situated in the wall of afferent arteriole just before it enters the bowman capsule. They are mostly present in the tunica media and tunica adventitia of the wall of afferent arteriole.

Functions of juxtaglomerular apparatus

1. Secretion of hormones like renin and prostaglandin
2. Regulation of glomerular blood flow and glomerular filtration rate.
3. **Role of Kidney in Regulation of 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 perfusion pressure directly regulates sodium excretion; a process known as pressure natriuretic, 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-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

1. **The role of kidney in Glucose 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.

* Hypocalcemia refers to low blood calcium concentration. Clinical signs of this disorder reflect increased neuromuscular excitability and include muscle spasms, tetany and cardiac dysfunction.
* 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.

**Body Distribution of Calcium and Phosphate**

There are three major pools of calcium in the body:

* **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.
* **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.
* **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:

* Stimulates production of the biologically-active form of vitamin D within the kidney.
* 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).
* 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:

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