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**DEPARTM**

**1. ROLE OF KIDNEY IN GLUCOSE HOMEOSTASIS**

Along with the liver, the kidney has important role in ensuring the energy needs during fasting periods. Some of the important roles’ includes;

1. The organ has a vital role in absorbing the entire quantity of the filtered glucose.
2. 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.
3. 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 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 the 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). Hyperglycemia 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 affect 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 glucogenic 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; renal gluconeogenesis, glycogenolysis, and glucose reabsorption.

**2. 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.

**STAGES OF MICTURITION**

The urinary bladder has two stages;

* **Resting or filling stage**: it is the 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 muscles. 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 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 sphincters are in a contracted state during the filling stage.

**PHYSIOLOGY OF MICTURITION**

The process of micturition is governed by both the nervous and muscular systems. Within the nervous system, the process is governed by the autonomous nervous system and the somatic system. Once the urinary bladder reaches its maximum capacity, the stretch receptors in the walls of the bladder send an impulse via the pelvic nerve to the brain via the spinal cord.

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 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.

**3. JUXTAGLOMERULAR APPARATUS**

Juxtaglomerular apparatus is a specialized organ situated near the glomerulus of each nephron (juxta = near).

The juxtaglomerular apparatus is formed by three different structures

1. **Macula densa**: it is the end portion of thick ascending segment before it opens into distal convoluted tubule. It is situated between afferent and efferent arterioles of the same nephron. It is very close to afferent arteriole. Macula densa plays an important role in tubuloglomerular feedback mechanismit also secretes thromboxane A2.
2. **Extraglomerular mesangial cells**: they are situated in the triangular region bound by afferent arterioles, efferent arteriole and macula densa. These cells are also called agranular cells, lacis cells or goormaghtigh cells. Extraglomerular mesangial cells secrete prostaglandin and cytokines.

**Glomerular mesangial cells**: besides extraglomerular mesangial cells, there is another type of mesangial cells situated in between glomerular capillaries called glomerular mesangial cells or intraglomerular mesangial cells. Glomerular mesangial cells support the glomerular capillary loops by surrounding the capillaries in the form of a cellular network. These cells play an important role in regulating the glomerular filtration by their contractile property. Glomerular mesangial cells are phagocytic in nature. These cells also secret glomerular intestinal matrix, prostaglandins and cytokines

1. **Juxtaglomerular cells**: these cells are specialized smooth muscle cells situated in then wall of the bowman’s capsule. These smooth muscle cells are mostly present in tunica media and tunica adventitia of the wall of the afferent arteriole. The juxtaglomerular cells are also called granular cells because of the presence of secretary granules in their cytoplasm. Juxtaglomerular cells form a thick cuff called polar cushion or polkissen around the afferent arteriole before it enters the bowman’s capsule.

**FUNCTIONS OF THE JUXTAGLOMERULAR APPARATUS**

Primary functions of juxtaglomerular apparatus include;

* **Secretion of hormones:**

Juxtaglomerular apparatus secretes two hormones:

1. **Renin**: juxtaglomerular cells secrete renin. Renin is a peptide with 340 amino acids. Along with angiotensin, renin forms the renin-angiotensin system, which is a hormone that plays an important role in the maintenance of blood pressure. Stimulants for renin secretion include;
2. Fall in arterial blood pressure
3. Reduction in the ECF volume
4. Increased sympathetic activity
5. Decreased load of sodium and chloride in macula densa
6. **Prostaglandins**: extraglomerular mesangial cells of juxtaglomerular apparatus secrete prostaglandin. Prostaglandin is also secreted by interstitial cells of medulla called type 1 medullary interstitial cells.

* **Secretion of other substance**:

1. Extraglomerular mesangial cells of juxtaglomerular apparatus secrete cytokines like interleukin-2 and tumor necrosis factor
2. Macula densa secretes thromboxane A2.

* Regulation of glomerular blood flow and glomerular filtration rate: macula densa of juxtaglomerular apparatus plays an important role in the feedback mechanism called tubuloglomerular feedback mechanism, which regulates the renal blood flow and glomerular filtration rate.

**4. 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 the 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, a hormone system that regulates blood pressure and water balance.

The blood pressure in the body depends on

1. The force by which the heart pumps out blood from the ventricles of the heart, and this is dependenton how much the inflowing blood into the ventricles.
2. The degree to which the arteries and arterioles constrict, this 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 the macula densa are located in a portion of the distal tubule located near and in the wall of the afferent arterioles. These cells sense the Na in the filtrate, while the arterial cells (juxtaglomerular cells) sense the blood pressure. When blood pressure is 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 into angiotensin-1. Angiotensin-1 is thereafter converted to angiotensin-2 by an angiotensin-converting enzyme, found in the lungs. Angiotensin-2 causes blood vessels to contract. The increased blood vessel constriction elevates the blood pressure. When the volume of blood is low, arterial cells in the secrete renin directly into circulation. Plasma renin then carries out the conversion of angiotensin-1. Angiotensin-1 is subsequently converted to angiotensin-2 by the 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 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, heart failure, kidney failure, and harmful effects of diabetes.

How the kidney increases circulating blood volume: angiotensin-2 also stimulates the adrenal gland to secrete a hormone called aldosterone. Aldosterone stimulates more Na reabsorption in the distal tubule, and water gets reabsorbed along with Na. the increases Na and water reabsorption from the distal tubule reduces urine output and increases the circulating blood volume. The increased blood volume helps stretch the heart muscle and causes it to generate more pressure with each beat, thereby increasing the blood pressure. The circulating blood volume is directly proportional to the stretch of the heart muscle.

The actions taken by the kidney to regulate blood pressure are especially important during traumatic injury, when they are necessary to maintain blood pressure and conserve the loss of fluids.

**5. ROLE OF KIDNEY IN CALCIUM HOMEOSTASIS**

The maintenance of calcium homeostasis is very important because calcium is the main component of boney skeleton and serves as the intracellular and extracellular messenger in numerous essential cellular events such as neuronal network, immune response, muscle contraction and hormone secretion. Total body calcium in the adult human is about 1-2kg and 99% of total calcium exists in bone.

About 50% of plasma calcium 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 200mg per day in an adult person with an average diet. Several factors are involved in the regulation of calcium in renal tubules. PTH (parathyroid hormone) and activated vitamin D enhance calcium reabsorption in the thick ascending limb, distal convoluted tubule and/or connecting tubule, and estrogen promotes calcium absorption in the distal convoluted tubule and connecting tubule.

Acidosis contributes to hypercalciuria by reducing calcium reabsorption in the proximal tubule and distal convoluted tubule, 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 controls renal calcium absorption through altered PTH secretion as well as via binding to the calcium sensing receptor (CaSR) in the TAL.

Only about 50 percent of the plasma calcium is ionized, with the remainder being bound to the plasmaproteins or complexed with anions such as phosphate. Therefore, only about 50 percent of the plasmacalcium can be filtered at the glomerulus. Normally, about 99 percent of the filtered calcium isreabsorbed by the tubules, with only about 1 percent of the filtered calcium being excreted. About 65percent of the filtered calcium is reabsorbed in the proximal tubule, 25 to 30 percent is reabsorbed inthe loop of Henle, and 4 to 9 percent is reabsorbed in the distal and collecting tubules. This pattern ofreabsorption is similar to that for sodium.

As is true with the other ions, calcium excretion is adjusted to meet the body's needs. With an increasein calcium intake, there is also increased renal calcium excretion, although much of the increase ofcalcium intake is eliminated in the feces. With calcium depletion, calcium excretion by the kidneysdecreases as a result of enhanced tubular reabsorption.

**PROXIMAL TUBULAR CALCIUM REABSORPTION**

Most of the calcium reabsorption in the proximal tubule occurs through the paracellular pathway,dissolved in water and carried with the reabsorbed fluid as it flows between the cells. Only about 20%of proximal tubular calcium reabsorption occurs through the transcellular pathway in two steps:

1. calcium diffuses from the tubular lumen into the cell down an electrochemical gradient due to the muchhigher concentration of calcium in the tubular lumen, compared with the epithelial cell cytoplasm, andbecause the cell interior has a negative relative to the tubular lumen;
2. calcium exits the cell acrossthe basolateral membrane by a calcium-ATPase pump and by sodium-calcium counter-transporter.

**LOOP OF HENLE AND DISTAL TUBULE CALCIUM REABSORPTION**

In the loop of Henle, calcium reabsorption is restricted to the thick ascending limb. Approximately 50%of calcium reabsorption in the thick ascending limb occurs through the paracellular route by passive diffusion due to the slight positive charge of the tubular lumen relative to the interstitial fluid. The remaining 50% of calcium reabsorption in the thick ascending limb occurs through the transcellular pathway, a process stimulated by parathyroid hormone (PTH)

In the distal tubule, calcium reabsorption occurs almost entirely by active transport through the cell membrane. The mechanism for this active transport is similar to that in the proximal tubule and thick ascending limb and involves diffusion across the luminal membrane through calcium channels and exit across the basolateral membrane by a calcium-ATPase pump, as well as a sodium-calcium counter transport mechanism. In this segment, as well as in the loops of Henle, PTH stimulates calciumreabsorption. Vitamin D (Calcitrol) and calcitonin also stimulate calcium reabsorption in the thick ascending limb of Henle's loop and in the distal tubule, although these hormones are not as important quantitatively as PTH in reducing renal calcium excretion.