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***17/MHS01/285***

***PHYSIOLOGY ASSIGNMENT***

**Question 1: Discuss the roles of the kidneys in glucose homeostasis.**

**Answer:**

The kidneys are involved in maintaining glucose homeostasis through three different mechanisms:

1. Production and release of glucose through

(a) Gluconeogenesis

(b) Glycogenolysis

2. Uptake and utilisation of glucose from the blood for it's own energy needs

3. Reabsorption of glucose from glomerular filtrate back into the blood

1.(a) **Renal Gluconeogenesis:**

Kidney produces glucose by gluconeogenesis in the renal cortex.

Gluconeogenesis involves formation of glucose-6-phosphate from precursors (lactate, amnio acids, glycerol) and subsequent conversion to free glucose.

The cells in the renal cortex have gluconeogenic enzymes and they can produce and release glucose into the circulation. 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.

(b) **Renal Glycogenolysis :**

Glycogenolysis involves the breakdown of glycogen to glucose-6-phosphate from precursors (e.g., lactate, glycerol, amino acids) and its subsequent hydrolysis (via glucose-6-phosphatase) to free glucose.

the liver and skeletal muscles contain most of the body’s glycogen stores, but only the liver contains glucose-6-phosphatase. As such, the breakdown or cleavage of hepatic glycogen leads to release of glucose, whereas the breakdown of muscle glycogen or glycogen from other sources can only release lactate. Lactate, that is generated via glycolysis( in blood cells, renal medulla, and other tissues) is often absorbed by other organs and helps in regenerating glucose.

2. **Uptake and utilisation of glucose from the blood for it's own energy needs:**

With regard to glucose utilization, the kidney may be perceived as 2 separate organs, with glucose utilization occurring predominantly in the renal medulla and glucose release limited to the renal cortex. These activities are separated as a result of differences in the distribution of various enzymes along the nephron. To this point, cells in the renal medulla (which, like the brain, are obligate users of glucose) have significant glucose-phosphorylating and glycolytic enzyme activity, and 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 free glucose into the bloodstream. On the other hand, renal cortex cells do possess gluconeogenic enzymes (including glucose-6-phosphatase), and therefore can produce and release glucose into the circulation. But because these cells have little phosphorylating capacity, they cannot synthesize glycogen.

3.  **Reabsorption of glucose from glomerular filtrate back into the blood:**

In addition to their important role in gluconeogenesis, the kidneys contribute to glucose homeostasis by filtering and reabsorbing glucose. Under normal conditions, the kidneys retrieve as much glucose as possible, rendering the urine virtually glucose free.

Approximately 180 grams of glucose are filtered by the glomeruli from plasma, daily but all of this quantity is reabsorbed through glucose transporter proteins that are present in cell membranes located within the proximal tubules. These transporters are sodium-glucose cotransporters (SGLT1 and SGLT2) expressed in S1 and S3 segments of proximal tubule. SGLT2 is the main sodium-glucose cotransporter responsible for 90% of glucose reabsorption.

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.

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.

**Question 2: Discuss the process of micturition**

**Answer:**

Micturition is the process of discharging urine from the urinary bladder. OR

Micturition is a process where urine is expelled from the body.

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 process consists of two phases:

1. Resting or filling/storage phase.

2. Voiding phase.

**Filling/storage Phase:**

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.

**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.

As mentioned earlier, 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 neural mechanism involved is called the 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 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: Explain juxtaglomerular apparatus**

**Answer:**

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. Their function remains unclear.

**Question 4: Discuss the roles of the kidneys in regulation of blood pressure**

**Answer:**

If a sudden change in blood pressure occurs it is controlled in the short term by the sympathetic nervous system which alters three things:

1. Total peripheral resistance

2. Capacitance

3. Cardiac output

It is only in the long term in response to chronic changes in blood pressure that the kidney works to alter the balance between fluid intake and output in order to regulate blood pressure.

Increased pressure has a direct effect on the kidney.

There are three mechanisms for the renal regulation of blood pressure. They are:

1. Pressure Diuresis

2. Pressure Natriuresis

3. Renin-Angiotensin-Aldosterone System

**Pressure Diuresis:**

As arterial blood pressure increases, the flow of blood through the kidneys also increases. This leads to an increase in filtration rate of the kidneys thereby increasing urinary output.

Also, when the body detects an increase in the blood pressure it inhibits the release of vasopressin (also known as antidiuretic hormone (ADH)), causing an increase in the production of urine.

**Pressure Natriuresis:**

If renal perfusion pressure is increased then sodium excretion increases I.e. sodium excretion increases when blood pressure increases.

As a result of the increase in excretion of sodium, less water is reabsorbed therefore the ECF volume decreases and blood pressure decreases.

The mechanism operates completely autonomously within the kidneys and independently of any external neurohormonal regulatory mechanisms. Its importance in connecting renal sodium transport to arterial pressure renders pressure natriuresis the dominant mechanism of both ECF volume regulation and systemic arterial pressure - long-term regulation.

**Renin-Angiotensin-Aldosterone System:**

Specialized cells in the distal tubule called the macula densa sense the concentration of sodium and chloride.

Decrease in blood pressure leads to a reduction in concentration of sodium and chloride in the distal tubule which is sensed by the macula densa.

The macula densa then releases prostaglandins which act on the juxtaglomerular apparatus thereby stimulating it to release renin into the bloodstream.

The drop in blood pressure is also detected by baroreceptors in the aortic arch, carotid sinus and the afferent renal arteriole which stimulates renin release by the juxtaglomerular apparatus.

Renin cleaves angiotensinogen into angiotensin 1 which in turn is cleaved by Angiotensin Converting Enzyme (ACE) into angiotensin 2.

Angiotensin 2 is a very potent vasoconstrictor and it also stimulates the adrenal cortex to release aldosterone.

Aldosterone acts on the distal tubules and collecting ducts in the kidney causing retention of sodium and water.

As a result of this, blood pressure increases.

**Question 5: Discuss the role of the kidneys in calcium homeostasis.**

**Answer:**

kidneys are major regulators of blood calcium level.

Parathyroid hormone increases the formation of 1, 25-dihydroxycholecalciferol from 25-hydroxycholecalciferol in the kidneys. The 1, 25-dihydroxycholecalciferol is an activated form of vitamin D. Vitamin D is necessary for the absorption of calcium from the intestines.