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**QUESTION 1**

Discuss the role of the kidneys in glucose homeostasis

**ANSWER**

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 fluctuations in glucose ingestion and glucose demands in various tissues. The kidneys are involved in maintaining glucose homeostasis through two different mechanisms, namely;

1. **Gluconeogenesis:** The kidney produces glucose by gluconeogenesis. The key enzymes responsible for this are expressed in the renal cortex only, specifically the proximal tubule. The kidneys produce between 2.0umol of glucose/kg/min thereby contributing about 20-25% of circulating glucose. The renal cortex is able to synthesize glucose-6-phosphatase from precursors (lactate, glycerol, alanine, glutamine) and is able to release glucose into the bloodstream
2. **Glucose filtration and reabsorption:** Plasma glucose is neither protein bound nor complexes with macromolecules and is therefore freely filtered at the glomerulus such that in normal individuals the renal glomeruli filters 180g of glucose per day. This would result in an enormous loss of glucose through the ultra-filtrate if not recovered, thus the kidney tries to regain as much glucose as possible and in normal situation almost all of it is reabsorbed in the proximal tubule by an insulin-independent process resulting in a virtually glucose free urine. Reabsorption of filtered glucose is by glucose transporters (mainly SGLT 1 & 2) that are present in the cell membranes of the proximal tubules. They have a limited capacity of reabsorption which when exceeded will lead to excretion of the rest via urine which would result in glycosuria. The maximum capacity is about 250-350mg/min. Renal reabsorption represents the main mechanism of glucose homeostasis by the kidney.

**QUESTION 2**

Discuss the process of micturition.

**ANSWER**

This is a process by which the urinary bladder empties when it becomes filled. It involves two main steps. The first step involves the progressive filling of the bladder until the tension in its walls reach a certain threshold eliciting the second step. The second step is the micturition reflex which causes the emptying of the bladder or at least causes a conscious desire to urinate.

**FILLING OF THE BLADDER**

As urine collects in the renal pelvis, the pressure in the pelvis increases and initiates a peristaltic contraction beginning in the pelvis and spreading along the ureter. This contraction forces urine into the bladder. The ureter enters obliquely into the bladder and the detrusor muscle of the bladder compresses it preventing reflux of urine.

**EMPTYING/ VOIDING OF THE BLADDER**

This is basically a reflex action called the micturition reflex, which is controlled by supra spinal reflexes and assisted by contraction of perineal and abdominal muscles.

**Micturition Reflex**

Micturition reflex is initiated by the stimulation of the stretch receptors located on the wall of the bladder and urethra. As the bladder fills with urine, once it reaches 300-400mL, the stretch receptors send sensory signals to the spinal cord via the pelvic nerves to reach the sacral micturition centre which is formed by the sacral detrusor nucleus and sacral pudendal nucleus. Efferent signals are then sent via parasympathetic fibres of the same nerve back to the bladder causing it to contract and internal sphincter causing its inhibition. Once the micturition reflex has been generated it is self-regenerative i.e. the initial contraction of the bladder will further activate the stretch receptors to increase its signals to the spinal cord which will cause further contraction of the bladder. This cycle continues until the bladder has reached a strong degree of contraction. Once the reflex becomes powerful enough, this will cause another reflex which passes through the pudendal nerve to the external sphincter causing its inhibition. If this inhibition is more potent than the voluntary constrictor signals from the brain urination will occur, if not urination will not occur and the reflex becomes more powerful.

**Facilitation and Inhibition of the Micturition Reflex**

The micturition reflex is an autonomic reflex; however it can be controlled by higher centres in the brain i.e. the cerebral cortex and the brainstem mainly the pons. In infants and children it is purely a reflex action. Voluntary control is gradually acquired as a learned ability and once acquired the higher centres exert control by the following means:

- The higher centres keep the micturition reflex partially inhibited except when desired.
- The higher centres (cortical centres) stimulate the sacral micturition centres to initiate the reflex action and also inhibits the external sphincter so that urination can occur
- The higher centres can prevent micturition even when the reflex occurs by tonic contraction of the external sphincter until urination is desired.

Certain muscular movements' aid emptying of the bladder, however it is not an essential component of the reflex, they are:

- The levator ani and perineal muscles relax and the post urethra shortens thereby decreasing urethral resistance.
- The diaphragm descends and the abdominal muscles contract accelerating the flow of urine by raising intra-abdominal pressure which in turn increase intra vesical pressure thereby increasing the flow of urine

**QUESTION 3**

Explain the juxtaglomerular apparatus

**ANSWER**

Juxtaglomerular (JG) apparatus as the name indicates (juxtanear) refers to the collection of specialised cells located very near to the glomerulus. It forms the major component of renin–angiotensin–aldosterone system. The Juxtaglomerular apparatus comprises of three types of cells which are

- Juxtaglomerular cells
- Macula densa cells
- Mesangial cells

**JUXTAGLOMERULAR CELLS**

Juxtaglomerular cells are specialised myoepithelial (modified vascular smooth muscle) cells located in the media of the afferent arteriole in the region of JG apparatus. Characteristic features of Juxtaglomerular cells are:

- They have well-developed Golgi apparatus and endoplasmic reticulum, abundant mitochondria and ribosomes.
- They synthesize, store and release an enzyme called *renin.* Renin is stored in the secretory granules of JG cells and, therefore, these are also called granular cells.
- They act as *baroreceptors* (tension receptors) and respond to changes in the transmural pressure gradient between the afferent arterioles and the interstitium.
- They are densely innervated by the sympathetic nerve fibres and release their renin content in response to the sympathetic discharge.
- As these cells act as vascular volume receptors, they monitor renal perfusion pressure and are stimulated by hypervolemia or decreased renal perfusion pressure.

**MACULA DENSA CELLS**

Macula densa cells refer to the specialised renal tubular epithelial cells of a short segment of the thick ascending limb of loop of Henle which passes between the afferent and efferent arterioles supplying its glomerulus of origin. Characteristic features of macula densa cells are:

- They are not well adapted for reabsorption.
- They are not innervated.
- These cells are in direct contact with the mesangial cells and in close contact with the Juxtaglomerular cells.
- They act as *chemoreceptors* and are stimulated by decreased NaCl concentration and thereby causing increased renin release.

**MESANGIAL CELLS**

Mesangial cells or *lacis* cells are the interstitial cells of the Juxtaglomerular apparatus. Characteristic features of these cells are:

- They are in contact with both the macula densa cells (on one side) and Juxtaglomerular cells (on the other side).
- Functionally, these cells possibly relay the signals from macula densa to the granular cells after modulating the signals. In this way, a decreased intraluminal $Na^+$ load, $Cl^-$ load, or both in the region of macula densa stimulates the juxtaglomerular cells to secrete renin.
- They also show granulation to secrete renin in conditions of extreme hyperactivity.
- They also secrete various substances and take up immune complexes.

**QUESTION 4**

Discuss the role of the kidneys in regulation of blood pressure

**ANSWERS**

The kidneys play an important main role in the long term control of blood pressure indirectly and directly by the following means:

- Renal body fluid feedback mechanism (directly)
- Renin-angiotensin system (indirectly)

**RENAL BODY FLUID FEEDBACK MECHANISM**

The most important mechanism for the long-term control of blood pressure is linked to control of circulatory volume by the kidney, a mechanism known as the **renal-body fluid feedback system**. In fact, it is similar to the capillary fluid shift mechanism except that only the renal glomerular capillaries are involved in the process.

The renal-body fluid system corrects the blood pressure by causing appropriate changes in the blood volume through *diuresis* and *natriuresis*.

**When blood pressure rises too high,** the kidneys excrete increased quantities of sodium and water because of *pressure natriuresis* and *pressure diuresis,* respectively. As a result of

increased renal excretion, the extracellular fluid volume and blood volume both decrease until blood pressure returns to normal and the kidneys excrete normal amounts of sodium and water.

**When the blood pressure falls too low,** the kidneys reduces the rate of sodium and water excretion, and over a period of hours to days, if the person drinks enough water and eats enough salt to increase blood volume, the blood pressure will return to its previous level. This mechanism being very slow to act is not of major importance in the acute control of arterial pressure. However, it is by far the most potent of all long-term arterial pressure controllers.

## RENIN-ANGIOTENSIN SYSTEM

The renin–angiotensin system has important roles in the regulation of blood pressure and in the regulation of extracellular fluid volume.

### Renin secretion and angiotensin formation

**Renin***,* a protease enzyme is secreted by the juxtaglomerular cells of the kidney into the blood. Its secretion is stimulated by a decrease in the blood pressure. Renin catalyses the conversion of **angiotensinogen** (α2-globulin substrate present in the plasma) to **angiotensin. Angiotensin I** is converted into **angiotensin II** by the action of *angiotensin converting enzyme* (ACE) present in the endothelium of blood vessels throughout the body, especially in the lungs and kidneys.

### Effects of angiotensin II

Angiotensin II has three principal effects by which it can elevate the arterial pressure:

1. **Vasoconstriction**: Angiotensin II is the most potent pressor substance being four to eight times more potent than norepinephrine. This effect of angiotensin II is important in the intermediate blood pressure control during circumstances, such as acute haemorrhage.
2. **Decrease in salt and water excretion by kidney:** Angiotensin II causes salt and water retention by the kidney. This action slowly increases extracellular fluid volume, which increases arterial pressure over a period of hours and days. Thus, this effect of angiotensin II plays an important role in the long-term control of arterial pressure. Angiotensin II causes salt and water retention by the kidney in two ways:

   **(i)** **By following direct actions on the kidneys:** Angiotensin II constricts the efferent arterioles which diminishes blood flow through the peritubular capillaries, allowing rapid osmotic reabsorption from the tubules. Angiotensin II directly stimulates the epithelial cells of renal tubules to increase reabsorption of sodium and water.

   **(ii)** **By stimulating secretion of aldosterone**: Angiotensin II stimulates the adrenal glands to secrete aldosterone which in turn increases salt and water reabsorption by the epithelial cells of the renal tubules.
3. **Stimulation of thirst:** Angiotensin II is a powerful stimulator of thirst. It leads to consumption of large volumes of water, leading to a rise in blood volume. This mechanism also plays some role in long-term control of blood pressure.

**QUESTION 5**

Discuss the role of the kidneys in calcium homeostasis

**ANSWER**

Calcium is both filtered and reabsorbed in the kidney but not secreted. Only about 60% of plasma calcium is ionized with the rest bound to plasma proteins and 10% complexed with anions such as phosphate. Therefore only about 60% of the plasma calcium can be filtered at the glomerulus. Normally about 99% of the filtered calcium is reabsorbed by the tubules, with only about 1% being excreted. 65% is absorbed at the proximal tubules, 25-30% at the loop of Henle and 4-9% at the distal collecting tubule. Calcium excretion is adjusted to meet the body needs, with an increase in calcium intake; there will be an increase in its excretion although much of calcium is eliminated in the faeces. With the depletion of calcium, its excretion by the kidney decreases as a result of enhanced tubular reabsorption.

One of the primary controllers of renal tubular calcium reabsorption is parathyroid hormone.

- Increased levels stimulate calcium reabsorption in the thick ascending loop of Henle and distal tubules which reduces urinary excretion of calcium. Conversely, reduction of Parathyroid hormone promotes calcium excretion by decreasing reabsorption. In the proximal tubule, calcium reabsorption usually parallel sodium and water reabsorption and is independent of parathyroid, therefore a decrease in sodium and water reabsorption will also lead to a decrease in calcium reabsorption and consequently increase urinary excretion of calcium.
- Increased plasma phosphate also stimulates parathyroid hormone and that leads to an increase in calcium reabsorption by the renal tubules thereby reducing calcium excretion. The opposite occurs with a reduction in plasma phosphate concentrations.
- Calcium reabsorption is also stimulated by metabolic alkalosis and inhibited by metabolic acidosis. Acidosis will increase calcium excretion and alkalosis will reduce calcium excretion. This effect is as a result of changes in the distal tubules.