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**PHYSIOLOGY ASSIGNMENT**

**COURSE TITLE: RENAL PHYSIOLOGY BODY FLUID AND TEMPERATURE REGULATION**

**COURSE CODE : PHS 303**

**QUESTION**

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**
6. The kidney along with the liver has an important role in ensuring the energy needs during fasting periods. This organ has a vital role in absorbing the entire quantity of filtered glucose. Having a glomerular filtration rate of 180 litres per day, it filters approximately 180 grams of glucose per day, bringing its contribution in maintaining normal fasting plasma glucose levels. The reabsorption of glucose is ensured by sodium-glucose cotransporter (SGLT2), responsible for the reabsorption of 90% of glucose and SGLT1, that reabsorbs the remaining glucose.

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. This can be explained by the need of the body to protect itself against hyper- and hypo- glycaemia. Hyperglycaemia is associated with both chronic effects (such as nephropathy, retinopathy and premature atherosclerosis) and also acute complications (including diabetic ketoacidosis and hyperosmolar hyperglycaemic states that are associated with higher morbidity and mortality). Hypoglycaemia 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 neuronal factors. In the acute phase, glucoregulatory mechanism 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 request and reabsorption into the general circulation of glucose from glomerular filtrate in order to preserve energy.

1. 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 the urethra. The urinary bladder can store around 350-400mlof urine before it expels it out.

STAGES OF MICTURITION

The urinary bladder has two distinct stages or places

1. Resting or filling stage
2. 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, 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 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.

1. The juxtaglomerular apparatus is a structure in the kidney that regulates the function of each nephron, the functional units of the kidney. The juxtaglomerular apparatus is named because it is next to the glomerulus.

The juxtaglomerular apparatus consists of three types of cells:

* The macula densa, a part of the distal convoluted tubule of the same nephron
* Juxtaglomerular cells which secrete renin
* Extraglomerular mesangial cells

 The juxtaglomerular apparatus is part of the kidney nephron, next to the glomerulus. It is found between afferent arteriole and the distal convoluted tubule of the same nephron. This location is critical to its functioning in regulating renal blood flow and glomerular filtration rate.

Renin is produced by juxtaglomerular cells. These cells are similar to epithelium and are located in the tunica media of the afferent arterioles as they enter the glomeruli. The juxtaglomerular cells secrete renin in response to:

* Stimulation of the beta-1 adrenergic receptor
* Decrease in renal perfusion pressure(detected directly by granular cells)
* Decrease in NaCl concentration at the macula densa, often due to a decrease in glomerular filtration rate.
1. The macula densa, a region of the distal convoluted tubule characterized by tubular epithelial cells which are more densely-packed than in other regions of the nephron(and thereby leading to its characteristic appearance on light microscopy). The macula densa can be considered the sensory arm of the renin-angiotensin-aldosterone axis in that these are the cells which sense decreased NaCl delivery which determines downstream function. They are also involved in the mechanism of tubloglomerular feedback.
2. The juxtaglomerular cells of the afferent arteriole, synthesize and store renin, which is secreted in response to specific stimuli (eg; low blood flow, decreased NaCl delivery). The juxtaglomerular cells could be considered the effector arm of the renin-angiotensin-aldosterone axis.
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) Discuss the role of kidney in regulation of blood pressure

The kidneys play a critical role in long term regulation of blood pressure. If a sudden change in blood pressure occurs it is controlled in the short term by the sympathetic nervous system which alters three things: total peripheral resistance, capacitance and 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.

Renal Regulation

Increased pressure has a direct effect on the kidney

 Q = (PA - PE) ÷ R

 Q = Flow, PA = Pressure in afferent arteriole, PE = Pressure in efferent arteriole, R = Resistance

Three mechanisms of renal regulation are:

A) Pressure Diuresis: As arteriolar blood pressure increases, so flow through the kidneys also increases which increases filtration rate and urinary output.

B) Pressure Natriuresis: If renal perfusion pressure is increased then sodium excretion increases i.e. sodium excretion increases when blood pressure increases. If more sodium is excreted less water is reabsorbed therefore the ECF volume decreases and blood pressure decreases. The actual mechanism is not clear but it is thought to involve a direct effect of the pressure on the renal interstitium.

C) Renin-Angiotensin-Aldosterone System: Specialized cells in the distal tubule called the macula densa sense the concentration of sodium and chloride. If blood pressure falls there is a reduction in concentration of sodium and chloride in the distal tubule which is sensed by the macula densa. The macula densa releases prostaglandins which act on the juxtaglomerular apparatus which releases 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 potent vasoconstrictor and 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. Blood pressure increases.

The Role of Renal Blood Flow

It is essential that renal blood flow is maintained to ensure that adequate filtration of toxins from the blood takes place. Changes in pressure affect renal blood flow. Important auto-regulatory processes are responsible for this.

The Role of Salt

Increasing the salt intake of an animal increases blood pressure in the short term. It increases the osmolarity of the blood which therefore increases water movement from tissues to the blood causing an increased circulating volume. As a result of this increased osmolarity more ADH is released as the osmoreceptors in the hypothalamus are triggered. This results in increased water retention in the kidneys further increasing the circulating volume. Secondary to the increase in salt the thirst centre is stimulated to increase fluid intake to try and counter act the increased osmolarity. This would increase blood volume and therefore pressure temporarily until this was corrected by the compensatory mechanisms.

5. Discuss the role of kidney in calcium homeostasis

Introduction

The maintenance of calcium homeostasis is very important because calcium is the main component of bony 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 1-2 kg and 99% of total calcium exists in bone. Even though only less than 1% of body calcium is in the extracellular space, maintaining the extracellular calcium concentration within a narrow range (8.5-10.5 mg/dL) is very important for calcium homeostasis. The kidney plays a key role in the fine regulation of calcium excretion.

Overview of Renal Ca2+ Handling

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 200 mg per day in an adult person with an average diet. Several factors are involved in the regulation of calcium in renal tubules. PTH and activated vitamin D enhance calcium reabsorption in the thick ascending limb (TAL), distal convoluted tubule (DCT) and/or connecting tubule (CNT), and oestrogen promotes calcium absorption in the DCT/CNT. Acidosis contributes to hypercalciuria by reducing calcium reabsorption in the proximal tubule (PT) and DCT, 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 also controls renal calcium absorption through altered PTH secretion as well as via binding to the calcium sensing receptor (CaSR) in the TAL. To facilitate Ca2+ reabsorption along renal tubules; (i) voltage difference between the lumen and blood compartment should be favourable for Ca2+ passage, i.e., a positive voltage in the lumen; (ii) concentration difference should be favourable for Ca2+ passage with a higher Ca2+ concentration in the lumen; (iii) an active transporter should exist if the voltage or concentration difference is not favourable for Ca2+ reabsorption. Each renal tubular segment has a different Ca2+ concentration difference or voltage environment for its unique mechanism for calcium reabsorption.

Renal Ca2+ handling along the tubules

Fifty to sixty percent of filtered calcium is absorbed in parallel with sodium and water in the PT, suggesting that the passive pathway is the main route of Ca2+ absorption in this segment. Claudin-2 is especially concentrated in the tight junction and also expressed in the basolateral membrane of the PT as the candidate for Para cellular Ca2+ channel in the PT. There is no evidence that Ca2+ reabsorption occurs in the thin descending and ascending limb. In the TAL, 15% of filtered calcium is absorbed, and the passive absorption through Para cellular space is known as the main mechanism. Paracellin-1 (claudin-16) is exclusively expressed in the tight junction of TAL and has been known as the important magnesium channel in the TAL. Paracellin-1 mutation caused hypercalciuria and nephrocalcinosis in addition to hypomagnesemia. This finding supports that paracellin-1 is not only the main Mg2+ channel, but also works as the paracellular Ca2+ channel in the TAL. There are some evidences that active transport occurs in the TAL, but no specific channel has yet been identified. The CaSR is a member of G protein-coupled receptors and suppresses PTH secretion by sensing high plasma Ca2+ level in the parathyroid glands. In the kidney, the CaSR is most highly expressed in the TAL. Familial hypocalciuric hypercalcemia (FHH) is an autosomal dominant disease due to the mutation of CaSR gene, and is manifested as hypercalcemia, hypophosphatemia, parathyroid hyperplasia, and unusually low renal clearance of calcium. Hypocalciuria, despite of hyperactivity of PTH in FHH, suggests that CaSR plays a direct role in Ca2+ absorption, especially in the TAL independent to PTH action.

Although only 10-15% of filtered Ca2+ is absorbed in the DCT and CNT, these are the main sites in which the fine regulation of Ca2+ excretion and the major action of PTH and activated vitamin D occur. In the DCT and CNT, the luminal voltage is negative and Ca2+ concentration in the lumen is lower than that of plasma. Thus, active transport mechanism against voltage and concentration gradient should exist in these segments. Several Ca2+ transporting proteins are involved in this active transmembrane transport of Ca2+ in the DCT and CNT. Transcellular Ca2+ reabsorption can occur by three steps; (i) entry of Ca2+ through the calcium channels (TRPV5, TRPV6) in the apical membrane, (ii) binding of Ca2+ with calciumbinding protein (calbindin) and diffusion in the cytoplasm (which enables no significant change in the intracellular i[Ca2+], and (iii) Ca2+ extrusion via an ATP-dependent plasma membrane Ca2+-ATPase (PMCA1b) and an Na2+/Ca2+ exchanger (NCX1) in the basolateral membrane. In the collecting duct (CD), there is no evidence that Ca2+ reabsorption occurs even though calcium channel (TRPV6) was documented to be expressed in CD cells. Each renal tubule has a unique environment and plays a different role in Ca2+ reabsorption. The coordinated play of different renal tubules could maintain harmony of renal Ca2+ handling.