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MEDICINE AND SURGERY

RENAL PHYSIOLOGY (PHS 303)

BODY FLUID AND TEMPERATURE REGULATION

1. DISCUSS THE ROLE OF KIDNEY IN GLUCOSE HOMEOSTASIS.

   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 [17]. 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. If the duration of fasting is increased, the glycogen stores are depleted and gluconeogenesis produces all the glucose released into 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 generated via glycolysis, is often absorbed by other organs and helps in regeneration of 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.

2. DISCUSS THE PROCESS OF MICTURITION.

Micturition is a process by which urine is voided from the urinary bladder. It is a reflex process. However, in grown up children and adults, it can be controlled voluntarily to some extent. The functional anatomy and nerve supply of urinary bladder are essential for the process of micturition.

Sensory (afferent) impulses from the receptors reach the sacral segments of spinal cord via the sensory fibers of pelvic (parasympathetic) nerve. Motor (efferent) impulses produced in spinal cord, travel through motor fibers of pelvic nerve towards bladder and internal sphincter. Motor impulses cause contraction of detrusor muscle and relaxation of internal sphincter so that, urine enters the urethra from the bladder. Once urine enters urethra, the stretch receptors in the urethra are stimulated and send afferent impulses to spinal cord via pelvic nerve fibers. Now the impulses generated from spinal centers inhibit pudendal nerve. So, the external sphincter relaxes and micturition occurs. Once a micturition reflex begins, it is self-regenerative, i.e. the initial contraction of bladder further activates the receptors to cause still further increase in sensory impulses from the bladder and urethra. These impulses, in turn cause further increase in reflex contraction of bladder. The cycle continues

repeatedly until the force of contraction of bladder reaches the maximum and the urine is voided out completely. During micturition, the flow of urine is facilitated by the increase in the abdominal pressure due to the voluntary contraction of abdominal muscles. Spinal centers for micturition are present in sacral and lumbar segments. But, these spinal centers are regulated by higher centers. The higher centers, which control micturition are of two types, inhibitory centers and facilitatory centers. Inhibitory centers for micturition centers in midbrain and cerebral cortex inhibit the micturition by suppressing spinal micturition centers. Facilitatory centers for micturition Centers in pons facilitate micturition via spinal centers. Some centers in cerebral cortex also facilitate micturition.

3. EXPLAIN THE JUXTAGLOMERULAR APPARATUS.

   Juxtaglomerular apparatus is a specialized organ situated near the glomerulus of each nephron. It is formed by three different structures: the macula densa, the extraglomerular mesangial cells and the juxtaglomerular cells. The macula densa 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 and is formed by tightly packed cuboidal epithelial cells. The extraglomerular mesangial cells are situated in the triangular region bound by afferent arteriole, efferent arteriole and macula densa. These cells are also called agranular cells, lacis cells or Goormaghtigh cells. The juxtaglomerular cells are specialized smooth muscle cells situated in the wall of afferent arteriole just before it enters the Bowman capsule. These smooth muscle cells are mostly present in tunica media and

tunica adventitia of the wall of the afferent arteriole. They are also called granular cells because of the presence of secretary granules in their cytoplasm. Besides extraglomerular mesangial cells there is another type of mesangial cells situated in between glomerular capillaries called glomerular mesangial 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. They are phagocytic in nature and also secrete glomerular interstitial matrix, prostaglandins and cytokines.

The primary function of the juxtaglomerular apparatus is the secretion of hormones: Renin and Prostaglandin mainly. Renin is secreted by renin juxtaglomerular cells. It is a peptide with 340 amino acids. Along with angiotensins, renin forms the renin-angiotensin system, which is a hormone system that plays an important role in the maintenance of blood pressure. Prostaglandin is secreted by extraglomerular mesangial cells of juxtaglomerular apparatus. It is also secreted by interstitial cells of medulla called type I medullary interstitial cells. The juxtaglomerular apparatus also secretes other substances apart from hormones. Extraglomerular mesangial cells of juxtaglomerular apparatus secrete cytokines like interleukin-2 and tumor necrosis factor. Macula densa secretes thromboxane A2.

Apart from secretion, the juxtaglomerular apparatus also regulates the glomerular blood flow and glomerular filtration rate. Macula densa of juxtaglomerular apparatus plays an important role in the feedback mechanism called tubulo-glomerular feedback mechanism, which regulates the renal blood flow and glomerular filtration rate.

4. DISCUSS THE ROLE OF KIDNEY IN REGULATION OF BLOOD PRESSURE.

The kidneys remove waste products and excess water from the body and so help to regulate 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. The three mechanisms of renal regulation include:

- **Pressure Diuresis**

  As arteriolar blood pressure increases, so flow through the kidneys also increases. This increases filtration rate and the urinary output.

- **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.

- **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.

5. DISCUSS THE ROLE OF KIDNEY IN CALCIUM HOMEOSTASIS.

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. Approximately 40% of plasma calcium is protein-bound and 10% of calcium is in a complex with anions like phosphate, citrate, and sulfate etc. Only half of plasma calcium is in its free form (ionized form, iCa2+) and physiologically important1). The ionized calcium is tightly regulated by hormones like parathyroid hormone (PTH), 1, 25-dihydroxyvitamin D3 (1, 25(OH) 2D3), calcitonin, and calcium itself. The kidney, intestine, and bone are the main target

organs of these regulators, and the kidney plays a key role in in the fine regulation of calcium excretion.

About 50% of plasma calcium (ionized and complex form; ultra-filterable fraction, excluding the protein bound form) 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. Parathormone and activated vitamin D enhance calcium reabsorption in the thick ascending limb (TAL), distal convoluted tubule (DCT) and/or connecting tubule (CNT), and estrogen promotes calcium absorption in the DCT/CNT1. 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 favorable for Ca2+ passage, i.e., a positive voltage in the lumen; (ii) concentration difference should be favorable 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 favorable for Ca2+ reabsorption. Each renal tubular segment has a different Ca2+ concentration difference or voltage environment for its unique mechanism for calcium reabsorption. The important renal calcium transport proteins are exclusively expressed in the DCT and CNT.

The kidneys filter 250 mmol of calcium ions a day in pro-urine (or glomerular filtrate), and resorbs 245 mmol, leading to a net average loss in the urine of about 5 mmol/d. The quantity of calcium ions excreted in the urine per day is partially under the influence of the plasma parathyroid hormone (PTH) level - high levels of PTH decreasing the rate of calcium ion excretion, and low levels increasing it. However, parathyroid hormone has a greater effect on the quantity of phosphate ions (HPO_4^{2-}) excreted in the urine. Phosphates form insoluble salts in combination with calcium ions. High concentrations of HPO_4^{2-} in the plasma, therefore, lower the ionized calcium level in the extra-cellular fluids. Thus, the excretion of more phosphate than calcium ions in the urine raises the plasma ionized calcium level, even though the total calcium concentration might be lowered.

The kidney influences the plasma ionized calcium concentration in yet another manner. It processes vitamin D3 into calcitriol, the active form that is most effective in promoting the intestinal absorption of calcium. This conversion of vitamin D3 into calcitriol, is also promoted by high plasma parathyroid hormone levels.

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. Urinary excretion of calcium is normally about 5 mmol (200mg) /day. This is less in comparison to what is excreted via the feces (15 mmol/day).