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Q1. The kidney is involved in the regulation of glucose homeostasis and in abnormalities found in diabetes mellitus via three different mechanisms:

 (i) Release of glucose into the circulation via gluconeogenesis;

(ii) Uptake of glucose from the circulation to satisfy its energy needs; and

(iii) Reabsorption into the circulation of glucose from glomerular filtrate to conserve glucose carbon

Renal Gluconeogenesis:

 For a really long time, it was believed that the liver is the major organ of gluconeogenesis under normal condition while kidney comes to play only when the body is in distress as in acidosis or prolonged starvation. This concept has however been challenged by recent studies and is found that kidney is as important as liver in post absorptive human state.

 In glucose homeostasis, the kidney may be considered as two different organs: the renal medulla and the renal cortex. This differentiation refers to the distribution of various enzymes in these parts of the kidney. Medulla holds enzymes for glucose phosphorylation, glycolysis and glycogen synthesis, but lacks glucose-6-phosphatase and gluconeogenic enzymes. Consequently, renal medulla satisfies its energy needs through glycolytic division of glucose, which produce lactate and synthesizes a small amount of glycogen for intracellular consumption. Given the lack of glucose-6-phosphatase, the renal medulla does not have the ability to release glucose into the circulation. On the other hand, the renal cortex holds gluconeogenic enzymes, synthesize glucose-6-phosphate from precursors; for instance, lactate, glutamine, glycerol, alanine and is able to release glucose into the blood stream via glucose-6-phosphatase.

Renal glucose utilization:

After an overnight fast, the kidneys use approximately 10% of all glucose utilized by the body. After meal ingestion, their glucose utilization increases in an absolute sense. In terms of whole-body glucose economy, normally approximately 45% of ingested glucose is thought to be converted to glycogen in the liver, 30% is taken up by skeletal muscle and later converted to glycogen, 15% is taken up by the brain, 5% is taken up by the adipose tissue and 10% is taken up by the kidneys. The metabolic fate of glucose is different in different regions of the kidney. Because of its low oxygen tension, and low levels of oxidative enzymes, the renal medulla is an obligate user of glucose for its energy requirement and does so anaerobically. Consequently, lactate is the main metabolic end product of glucose taken up in the renal medulla. In contrast, the renal cortex has little glucose phosphorylating capacity but a high level of oxidative enzymes. Consequently, this part of the kidney does not take up and use very much glucose, with oxidation of FFAs acting as the main source of energy. A major energy-requiring process in the kidney is the reabsorption of glucose from glomerular filtrate in the proximal convoluted tubule.

Renal glucose absorption:

In addition to releasing glucose into the circulation by synthesizing new glucose molecules via gluconeogenesis and its utilization of glucose, the kidney can also influence glucose homeostasis by returning glucose to the circulation via the reabsorption of glucose from glomerular filtrate. As the average plasma glucose concentration throughout a 24h period is 5.5 mmol/l (100 mg/dl), approximately 180 g of glucose is filtered by the kidneys each day. In healthy individuals, virtually all of this is reabsorbed into the circulation and the urine is essentially free from glucose. To put this into perspective, in a given day, the kidneys produce 15–55 grams of glucose via gluconeogenesis and metabolize 25–35 grams of glucose. Therefore, in terms of glucose economy, it is clear that renal reabsorption is the primary mechanism by which the kidney influences glucose homeostasis. Alterations in renal tubular glucose reabsorption may therefore be expected to have a considerable impact on glucose homeostasis.

Reabsorption of glucose from glomerular filtrate occurs by means of sodium–glucose co-transporters (SGLTs) in the proximal convoluted tubule. In animal models, approximately 90% of glucose is reabsorbed by SGLT2, a high-capacity low-affinity glucose transporter. SGLT2 is thought to be located exclusively on the luminal surface of the epithelial cells lining the S1 and S2 segments of the proximal tubule. Transport of sodium and glucose by SGLT2 occurs in a 1:1 ratio. The remaining 10% of glucose reabsorption is mediated by SGLT1, a high-affinity, low-capacity glucose/galactose transporter; sodium:glucose coupling ratio = 2:1 located on the luminal surface of epithelial cells lining the S3 segment of the proximal tubule. SGLT1 is also extensively expressed in the small intestine and in other tissues. Glucose reabsorbed from the proximal tubules by SGLTs is then released into the circulation through the action of facilitative glucose transporters (GLUTs) at the basolateral membrane of the epithelial cells lining the proximal tubules (GLUT2 in the S1/2 segments and GLUT1 in the S3 segment). SGLT-mediated glucose transport is an active process, moving glucose against a concentration gradient, utilizing energy derived from the sodium electrochemical potential gradient across the brush border membrane and maintained by the transport of intracellular sodium into the blood via sodium:potassium adenosine triphosphatase (ATPase) pumps at the basolateral membrane. In contrast, GLUTs facilitate passive transport (equilibration) of glucose across membranes and do not require an energy source

Q3. The juxtaglomerular apparatus is a microscopic structure in the kidney, which regulates the function of each nephron. The juxtaglomerular apparatus is so called because of its proximity to the glomerulus: it is found between the vascular pole of the renal corpuscle and the returning distal convoluted tubule of the same nephron. This location is critical to its function in regulating renal blood flow and glomerular filtration rate. The three cellular components of the apparatus are the macula densa of the distal convoluted tubule, smooth muscle cells of the afferent arteriole and juxtaglomerular cells.

Juxtaglomerular cells

Juxtaglomerular cells are modified pericytes of glomerular arterioles. They are sometimes called granular cells because they become granulated as they release renin).The juxtaglomerular cells secrete renin in response to: Beta-1 adrenergic stimulation

Decrease in renal perfusion pressure (detected directly by the granular cells)

Decrease in NaCl concentration at the macula densa, often due to a decrease in glomerular filtration rate, resulting in slower filtrate movement through the proximal tubule and thus more time for reabsorption.

Macula Densa Cells

Macula densa cells are columnar epithelium thickening of the distal tubule. The macula densa senses any increase in the sodium chloride concentration in the distal tubule of the kidney and secretes a locally active (paracrine) vasopressor which acts on the adjacent afferent arteriole to decrease glomerular filtration rate (GFR), as part of the tubuloglomerular feedback loop.

Specifically, excessive filtration at the glomerulus or inadequate sodium uptake in the proximal tubule / thick ascending loop of Henle brings to the distal convoluted tubule fluid that has an abnormally high concentration of sodium. Apical NaK2Cl cotransporters move sodium into the cells of the macula densa. The macula densa cells do not have enough basolateral Na/K ATPases to excrete this added sodium, so the cell's osmolarity increases. Water flows into the cell to bring the osmolarity back down, causing the cell to swell. When the cell swells, a stretch-activated non-selective anion channel is opened on the basolateral surface. ATP escapes through this channel and is subsequently converted to adenosine. Adenosine vasoconstricts the afferent arteriole via A1 receptors and vasodilates (to a lesser degree) efferent arterioles via A2 receptors, which decreases GFR. Also, adenosine inhibits renin release in JG cells via A2 receptors on JG cells using a Gi pathway.

Additionally, when macula densa cells detect higher concentrations of Na and Cl they inhibit nitric oxide synthetase (decreasing renin release) by an unknown pathway.

A decrease in GFR means less solute in the tubular lumen. As the filtrate reaches the macula densa, less NaCl is reabsorbed. The macula densa cells detect lower concentrations of Na and Cl and upregulate nitric oxide synthetase (NOS). NOS creates nitric oxide (NO) which catalyses the formation of prostaglandins. These prostaglandins diffuse to the granular cells and activate a prostaglandin-specific Gs receptor. This receptor activates adenylate cyclase, which increases levels of cAMP. cAMP augments renin release. Prostaglandins and NO also vasodilate the afferent arterioles. Efferent arterioles are spared from this effect by renin release.

Q2. Micturition is the process by which the urinary bladder empties when it becomes filled. This process involves two main steps: first the bladder fills progressively until the tension in its well rises above a threshold level. This tension elicits the the second step which is a nervous reflex called micturition reflex that empties the bladder or, if this fails, at least causes a conscious desire to urinate. Although the micturition reflex is an autonomic spinal cord reflex, it can also be inhibited or facilitated by centres in the cerebral cortex or brain stem.

As the bladder fills, many superimposed micturition contractions begin to appear. These are a result of a stretch reflex initiated by sensory stretch receptors in the bladder wall, especially by the receptors in the posterior urethra when this area begins to fill with urine at the higher bladder pressures. Sensory signals from the bladder stretch receptors are conducted to the sacral segments of the cord through the pelvic nerves and then reflexively back again to the bladder through parasympathetic nerve fibres by way of the same nerves. When the bladder is partially filled, these contractions usually relax spontaneously after a fraction of a minute, the detrusor muscles stop contracting and pressure falls back to the baseline. As the bladder continues to fill, the micturition reflex becomes more frequent and causes greater contractions of the detrusor muscles

once a micturition reflex begins, it is self-regenerative .This means that the initial contraction of the bladder activates the stretch receptors to cause a greater increase in sensory impulses from the bladder and posterior urethra, which causes a further increase in reflex contraction of the bladder; thus, the cycle is repeated continuously until the bladder reaches a strong degree of contraction. Then, after a few seconds to more than a minute, the self-regenerative reflex begins to fatigue and the regenerative cycle of the micturition reflex ceases, permitting the bladder to relax

0nce a micturition reflex has occurred but not succeeded in emptying the bladder, the nervous elements of this reflex usually remain in an inhibited state for a few minutes to 1hr or more before another micturition reflex occurs. As the bladder becomes more and more filled, these reflexes occur more often and more powerfully.

Once the micturition reflex becomes powerful enough, it causes another reflex, which passes through the pudendal nerves to the external sphincter to inhibit it. If this inhibition is more potent in the brain than the voluntary constrictor signals to the external sphincter, urination will occur. If not urination will not occur until the bladder fills still further and the micturition reflex becomes more powerful

Q5. **CALCIUM HOMEOSTASIS**

 Calcium is both filtered and absorbed in the kidney but not secreted. Making the rate of renal calcium excretion calculated as; renal calcium excretion= calcium filtered- calcium reabsorbed

About 60% of plasma calcium is ionized, with 40% being bound to plasma proteins and 10% complexed with anions such as phosphate. Therefore, only about 60% of the plasma calcium is filtered at the glomerulus. Normally, about 90% of filtered calcium is reabsorbed by the tubules, with only about 1% of the filtered calcium being excreted. About 65% of the filtered calcium is reabsorbed in the proximal tubule, 25-30% is reabsorbed in the loop of henle, and 4 to 9% is reabsorbed in the distal and collecting tubules. This pattern of reabsorption is similar to that of sodium.

Calcium excretion is adjusted to meet the body’s needs. With an increase in calcium intake, there’s also an increased renal calcium excretion, although much of the increase of calcium intake is eliminated in the faeces. With calcium depletion, calcium excretion by the kidneys decreases a result of enhanced tubular reabsorption

Two main transepithelial calcium transport pathways have been described along the tubules of the kidneys: paracellular and transcellular. Paracellular pathways are dependent on transepithelial electrochemical gradients and can be regulated by specialized paracellular proteins, the claudins. The transcellular path implies the presence of a tight epithelium and a three-step transport with apical entry, transcytoplasmic transport, and basolateral extrusion mechanisms. The driving force is mainly provided by basolateral Ca- or Na-K-ATPases.

Proximal tubular calcium reabsorption: Most of calcium reabsorption in the PT occurs through the paracellular pathway; it is 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 much higher concentration of calcium in the tubular lumen, compared with the epithelial cell cytoplasm, and also because thecell interior has a negative charge relative to the tubular lumen

2) Calcium exits the cell across the 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, ccalcium reabsorption is restricted to the thick ascending limb. Approximately 50% of calcium reabsorption in the thick ascending limb occurs through 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. It is stimulated by the parathyroid hormone.

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 the loops of henle, PTH stimulates calcium reabsorption , Vit. D(CALCITROL) and calcitonin also stimulate calcium reabsorption in the thick ascending limb of henle’s loop and the distal tubule although these hormones are not as important quantitatively as PTH in reducing calcium excretion.

Q4. The kidneys play a fundamental role in the long-term control of arterial pressure by regulating sodium balance and extracellular fluid volume. The renin-angiotensin system (RAS) is at the center of the regulation of hypertension and progressive renal injury and also fluid balance in the body. When blood volume or sodium levels in the body are low, or blood potassium is high, cells in the kidney release the enzyme, renin. Renin converts angiotensinogen, which is produced in the liver, to the hormone angiotensin I. An enzyme known as ACE or angiotensin-converting enzyme found in the lungs metabolizes angiotensin I into angiotensin II. Angiotensin II causes blood vessels to constrict and blood pressure to increase. Angiotensin II stimulates the release of the hormone aldosterone in the adrenal glands, which causes the renal tubules to retain sodium and water and excrete potassium. Together, angiotensin II and aldosterone work to raise blood volume, blood pressure and sodium levels in the blood to restore the balance of sodium, potassium, and fluids. If the renin-angiotensin system becomes overactive, consistently high blood pressure results.

 Another way in which the kidneys maintain blood pressure is through the regulation of the volume of blood in the body. One of the major roles of the kidneys is maintaining the proper levels of electrolytes (such as sodium and potassium) in the body. The amount of electrolytes in the body influences the amount of fluid in the body. When electrolyte levels are high, the body retains more water, which in turn increases the volume of the blood. More blood volume results in higher blood pressure. Thus, the kidneys maintain blood pressure by indirectly controlling the amount of blood in the body.