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**QUESTION 1**

1. **ROLE OF KIDNEY IN GLUCOSE HOMEOSTASIS**

***Glycogenolysis and Gluconeogenesis***  
Renal release of glucose into the circulation is the result of glycogenolysis and gluconeogenesis. Glycogenolysis involves the breakdown of glycogen to glucose-6-phosphate from precursors (eg, lactate, glycerol, amino acids) and its subsequent hydrolysis (via glucose-6-phosphatase) to free glucose. Conversely, gluconeogenesis involves formation of glucose-6-phosphate from those same precursors and subsequent conversion to free glucose. Interestingly, 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 of hepatic glycogen leads to release of glucose, whereas the breakdown of muscle glycogen leads to release of lactate. Lactate (generated via glycolysis of glucose by blood cells, the renal medulla, and other tissues) may be absorbed by organs and reformed into glucose.  
  
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 and accumulate glycogen. However, since these cells lack glucose-6-phosphatase and other gluconeogenic enzymes, they cannot release free glucose into the circulation. On the other hand, renal cortex cells do possess gluconeogenic enzymes (including glucose-6-phosphatase), and therefore can make and release glucose into the circulation. But because these cells have little phosphorylating capacity, they cannot synthesize glycogen.  
  
  
***Glucose Reabsorption***  
  
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. The glomeruli filter from plasma approximately 180 grams of D-glucose per day, all of which is reabsorbed through glucose transporter proteins that are present in cell membranes within the proximal tubules. This would result in an enormous loss of glucose through the ultrafiltrate if not recovered; thus, the main physiological undertaking of the kidney is to regain as much glucose as possible, and in normal situations almost all of it is reabsorbed in the proximal tubule by an insulin-independent process. The ability of the proximal tubule to reabsorb glucose amplifies as the filtered load is increased by either an elevation in plasma glucose or an increase in glomerular filtration rate. This enhancement eventually reaches a threshold (Tm glucose) that represents the maximal reabsorptive capacity of the proximal tubule and increases in the filtered load above this point results in glycosuria. If the capacity of these transporters is exceeded, glucose appears in the urine. This maximum capacity, known as the tubular maximum for glucose (TmG), ranges from 260 to 350 mg/min/1.73 m2 in healthy adults and children, and corresponds to a plasma glucose level of approximately 200 mg/dL.Once the TmG (the threshold) is reached and transporters are unable to reabsorb all the glucose (as in T2DM), glucosuria ocurrs.The correlation between the degree of hyperglycemia and degree of glucosuria becomes linear when blood glucose concentrations have increased beyond a threshold. It should be noted that slight differences between individual nephrons and the imprecise nature of biological systems may alter this linear concentration/reabsorption curve, as indicated by a splay from the theoretical as the TmG is approached. As such, glucosuria may potentially develop before the expected TmG is reached. Glucosuria may also occur at lower plasma glucose concentrations in certain conditions of hyperfiltration (eg, pregnancy), but as a consequence of hyperfiltration rather than significant hyperglycemia. When the glomerular filtration rate is normal, the level of plasma glucose that results in glycosuria is B11 mM; however, when glomerular filtration rate increases in situations such as pregnancy or a unilateral kidney, glycosuria will occur at lower plasma glucose levels. Conversely, in the case of reduced glomerular filtration rate such as in chronic kidney disease, glycosuria would be absent until levels of plasma glucose are higher.

**Renal Glucose Transporters**

The transport of glucose (a polar compound with positive and negative charged areas, making it soluble in water) into and across cells is dependent on specialized carrier proteins in 2 gene families: the facilitated glucose transporters (GLUTs) and the sodium-coupled glucose cotransporters (SGLTs). These transporters control glucose transport and reabsorption in several tissue types, including the proximal renal tubule, small intestine, blood-brain barrier, and peripheral tissues. GLUTs are involved in the passive transport of glucose across cell membranes, facilitating its downhill movement as it equilibrates across a membrane. SGLTs, on the other hand, mediate active transport of glucose against a concentration gradient by means of cotransport with sodium. Of the various SGLT proteins expressed in the kidneys, SGLT2 is considered most important; based on animal studies, it is responsible for reabsorbing 90% of the glucose filtered at the glomerulus. SGLT1 contributes to the other 10% of glucose reabsorbed in the proximal tubule. This predominant role of SGLT2 in renal reabsorption of glucose raises the prospect of therapeutically blocking this protein in patients with diabetes. Of the various GLUT proteins expressed in the kidneys, GLUT2 is the major transporter, releasing into circulation the glucose reabsorbed by SGLTs in the proximal tubular cells.

**QUESTION 2**

1. **Micturition**

Micturition or urination is the process of expelling urine from the bladder. This act is also known as voiding of the bladder. 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. 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.

The urinary bladder can store around 350-400ml of urine before it expels it out.

**Stages of Micturition**

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.

**QUESTION 3**

1. **JUXTAGLOMERULAR APPARATUS**

The juxtaglomerular apparatus lies between the glomerulus and the distal convoluted tubule of the same nephron. This location is critical to its function in regulating renal blood flow and thus the glomerular filtration rate (GFR). The juxtaglomerular apparatus consists of three cell types: the macula densa cells, the juxtaglomerular cells and the extraglomerular mesangial cells.

**The Macula Densa**

The macula densa cells of the distal convoluted tubule are smaller than the usual cuboidal cells of the tubule and packed rather closely together. They may be recognized by their close packing and dark staining nuclei. These cells appear to have a different morphological polarity from the adjacent cuboidal cells: the Golgi apparatus lies between the nuclei and the bases of the cells. Beneath the macula densa cells, the basal lamina is thin with extensions from the cells passing through it. It is thought that the macula densa cells are sensory cells that respond to the sodium concentration in the fluid within the distal tubule and, perhaps, to the rate of fluid flow past them. An increase in sodium concentration in the tubular fluid leads to a reduction in the production of renin by extra glomerular mesangial cells and juxtaglomerular cells.

**Juxtaglomerular cells**

The juxtaglomerular cells secrete renin, and as specialized smooth muscle cells surrounding the afferent arteriole also have the capacity to affect the perfusion of the glomerulus. Although they are activated by prostaglandins released from the macula densa cells, they can also release renin independently of the macula densa. Baroreceptors found in the arterioles trigger renin secretion if there is a fall in blood pressure in the arterioles. Activation of the sympathetic nervous system can also stimulate renin release through activation of beta-1 receptors. Renin is a protease enzyme that catalyses the conversion of angiotensinogen to angiotensin I. Angiotensin I is converted into the active vasoconstrictor angiotensin II by Angiotensin Converting Enzyme (ACE) found in the kidney and largely in the lung.

**Extra glomerular Mesangial Cells**

Extra glomerular mesangial cells, also known as lacis cells or Goormaghtigh cells, are located in the space between the afferent and efferent arterioles, and the glomerular capillaries. These pale staining, renin containing cells are located just outside the glomerulus, near the vascular pole. They are a type of smooth muscle cell, and although their function is yet to be fully clarified, they play a role in autoregulation of blood flow to the kidney and regulation of systemic blood pressure through the renin-angiotensin system.

**QUESTION 4**

1. **ROLE OF KIDNEY IN REGULATION OF BLOOD PRESSURE**

**The Renin-Angiotensin-Aldosterone System (RAAS)** is a hormone system within the body that is essential for the regulation of blood pressure and fluid balance. The system is mainly comprised of the three hormones **renin**, **angiotensin II** and **aldosterone**. Primarily it is regulated by the rate of **renal blood flow**.

**Renin Release**

The first stage of the RAAS is the release of the enzyme **renin**. Renin released from granular cells of the renal **juxtaglomerular apparatus** (JGA) in response to one of three factors:

* Reduced sodium delivery to the distal convoluted tubule detected by **macula densa** cells.
* Reduced perfusion pressure in the kidney detected by **baroreceptors** in the afferent arteriole.
* Sympathetic stimulation of the JGA via β1 adrenoreceptors.

The release of renin is inhibited by **atrial natriuretic peptide**(ANP), which is released by stretched atria in response to increases in blood pressure.

**Production of Angiotensin II**

**Angiotensinogen** is a precursor protein produced in the liver and cleaved by **renin** to form angiotensin I.

Angiotensin I is then converted to angiotensin II by **angiotensin converting enzyme** (ACE). This conversion occurs mainly in the **lungs** where ACE is produced by vascular endothelial cells, although ACE is also generated in smaller quantities within the renal endothelium.

**Binding of Angiotensin II**

**Angiotensin II** exerts its action by binding to various receptors throughout the body. It binds to one of two G-protein coupled receptors, the AT1 and AT2 receptors. Most actions occur via the AT1 receptor.

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**Effects of Angiotensin II**

**Cardiovascular Effects**

Angiotensin 2 acts on **AT1 receptors** found in the endothelium of arterioles throughout the circulation to achieve **vasoconstriction**. This signalling occurs via a **Gq** protein, to activate phospholipase C and subsequently increase intracellular calcium.

The net effect of this is an increase in **total peripheral resistance** and consequently, blood pressure.

**Neural Effects**

Angiotensin II acts at the **hypothalamus** to stimulate the sensation of thirst, resulting in an increase in fluid consumption. This helps to raise the circulating volume and in turn, blood pressure. It also increases the **secretion of ADH** from the posterior pituitary gland – resulting in the production of more concentrated urine to reduce the loss of fluid from urination. This allows the circulating volume to be better maintained until more fluids can be consumed. Further information on **ADH** can be found here.

It also stimulates the sympathetic nervous system to increase the release of noradrenaline (NA)**.** This hormone is typically associated with the “fight or flight” response in stressful situations and has a variety of actions that are relevant to the RAAS:

* Increase in cardiac output.
* Vasoconstriction of arterioles.
* Release of renin.

The renin-angiotensin system or RAS regulates blood pressure and 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.

**QUESTION 5**

1. **ROLE OF THE KIDNEYS IN CALCIUM HOMEOSTASIS**

The **kidney** is critcally important in calcium homeostasis. 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.

There are three major pools of calcium in the body:

* **Intracellular calcium:** A large majority of calcium within cells is sequestered in mitochondria and endoplasmic reticulum. Intracellular free calcium concentrations fluctuate greatly, from roughly 100 nM to greater than 1 uM, due to release from cellular stores or influx from extracellular fluid. These fluctuations are integral to calcium's role in intracellular signaling, enzyme activation and muscle contractions.
* **Calcium in blood and extracellular fluid:** Roughly half of the calcium in blood is bound to proteins. The concentration of ionized calcium in this compartment is normally almost invariant at approximately 1 mM, or 10,000 times the basal concentration of free calcium within cells. Also, the concentration of phosphorus in blood is essentially identical to that of calcium.
* **Bone calcium:** A vast majority of body calcium is in bone. Within bone, 99% of the calcium is tied up in the mineral phase, but the remaining 1% is in a pool that can rapidly exchange with extracellular calcium.

**Hormonal Control Systems**

Maintaining normal blood calcium and phosphorus concentrations is managed through the concerted action of three hormones that control fluxes of calcium in and out of blood and extracellular fluid:

**Parathyroid hormone serves to increase blood concentrations of calcium.** Mechanistically, parathyroid hormone preserves blood calcium by several major effects:

* Stimulates production of the biologically-active form of vitamin D within the kidney.
* Facilitates mobilization of calcium and phosphate from bone. To prevent detrimental increases in phosphate, parathyroid hormone also has a potent effect on the kidney to eliminate phosphate (phosphaturic effect).
* Maximizes tubular reabsorption of calcium within the kidney. This activity results in minimal losses of calcium in urine.

**Vitamin D acts also to increase blood concentrations of calcium.** It is generated through the activity of parathyroid hormone within the kidney. Far and away the most important effect of vitamin D is to facilitate absorption of calcium from the small intestine. In concert with parathyroid hormone, vitamin D also enhances fluxes of calcium out of bone.

**Calcitonin** is a hormone that functions to reduce blood calcium levels. It is secreted in response to hypercalcemia and has at least two effects:

* Suppression of renal tubular reabsorption of calcium. In other words, calcitonin enhances excretion of calcium into urine.
* Inhibition of bone resorption, which would minimize fluxes of calcium from bone into blood.