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**Question One: Discuss the role of kidney in glucose homeostasis**

The most well-understood property of the nephron is its ability to transport substances by different mechanisms. Most transport in the nephron uses membrane proteins and exhibits the three characteristics of mediated transport: saturation, specificity, and competition.

Glucose reabsorption in the nephron is an excellent example of the consequences of saturation. At normal plasma concentrations, all glucose that enters the nephron is reabsorbed before it reaches the end of the proximal tubule. The tubule epithelium is well supplied with carriers to capture glucose as the filtrate flows past. If the blood glucose concentration becomes excessive, glucose will be filtered faster than the carriers can absorb it. The carriers will become saturated and unable to reabsorb all the glucose that flows to the tubule. The transport rate at saturation is called the transport maximum, known as Tm. As a result, some glucose escapes reabsorption and is excreted in the urine.

The kidney contributes to glucose homeostasis through processes of gluconeogenesis, glucose filtration, glucose reabsorption, and glucose consumption. Each of these processes can be altered in patients with type-2 diabetes, providing potential targets for novel therapies.

Under normal circumstances, up to 180 g/day of glucose is filtered by the renal glomerulus and virtually all of it is subsequently reabsorbed in the proximal convoluted tubule. This reabsorption is effected by two sodium-dependent glucose cotransporter (SGLT) proteins which absorb across the apical lumen. SGLT2, situated in the S1 segment, is a low-affinity high-capacity transporter reabsorbing up to 90% of filtered glucose. SGLT1, situated in the S3 segment, is a high-affinity low-capacity transporter reabsorbing the remaining 10%. Glucose is also exit the tubular cells, by GLUT2 uniport proteins across the basolateral membrane.

**Question Two: Discuss the process of micturition**

Micturition is the ejection of urine from the urinary bladder through the urethra to the outside of the body. Physiologically, micturition involves the coordination of the central, autonomic, and somatic nervous systems. The brain centers that regulate urination include the pontine micturition center, the periaqueductal gray, and the cerebral cortex, which cause both involuntary and voluntary control over micturition.

In males, urine is ejected through the penis, and in females through the urethral opening. Due to sexual dimorphism, and the positions where the urethra ends, males and females often use different techniques for urination. Micturition consists of two phases:

* The storage phase: A relaxed bladder in which urine slowly fills the bladder.
* The voiding phase: A contracted bladder that forces the external sphincter open and discharges urine through the urethra.

The muscles controlling micturition are controlled by the autonomic and somatic nervous systems, which open the two sphincters during the voiding phase of micturition. During the storage phase the internal urethral sphincter is tense and the detrusor muscle is relaxed by sympathetic stimulation. During the voiding phase of micturition, parasympathetic stimulation causes the internal urethral sphincter to relax. The external urethral sphincter (sphincter urethrae) is under somatic control and is consciously relaxed (and thus opened) during micturition. Many males prefer to urinate standing. In females, the urethra opens straight into the vulva. Because of this, the urine often does not exit at a distance from the body and is therefore seen as harder to control.

The Micturition Reflex

The state of the micturition reflex system is dependent on both a conscious signal from the brain and the firing rate of sensory stretch fibers from the bladder and urethra. At low bladder volumes, the afferent firing of the stretch receptors is low, and results in relaxation of the bladder. At high bladder volumes, the afferent firing of the stretch receptors increases, and causes a conscious sensation of urinary urge. This urge becomes stronger as the bladder becomes more full.

The micturition reflex causes bladder contraction during voiding, through a neural pathway. This reflex may lead to involuntary micturition in individuals that may not be able to feel the sensation of urinary urge, due to the firing of the stretch receptors themselves.

**Question Three: Explain juxtaglomerular apparatus**

The **juxtaglomerular apparatus** (also known as the **juxtaglomerular complex**) 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 (juxta-) the glomerulus.

The juxtaglomerular apparatus consists of three types of cells:

1. the macula densa, a part of the distal convoluted tubule of the same nephron
2. juxtaglomerular cells, (also known as granular cells) which secrete renin
3. 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 function in regulating renal blood flow and glomerular filtration rate.

**Functions**

Juxtaglomerular Apparatus

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.[[2]](https://en.wikipedia.org/wiki/Juxtaglomerular_apparatus#cite_note-ganong-2) The juxtaglomerular cells secrete renin in response to:

* Stimulation of the beta-1 adrenergic receptor
* 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

Extraglomerular Mesangial Cells

Extraglomerular mesangial cells are located in the junction between the afferent and efferent arterioles. These cells have a contractile property similar to vascular smooth muscles and thus play a role in “regulating GFR” by altering the vessel diameter. Renin is also found in these cells.

Macula Densa

At the point where the afferent arterioles enter the glomerulus and the efferent arteriole leaves it, the tubule of the nephron touches the arterioles of the glomerulus from which it rose. At this location, in the wall of the distal convoluted tubule, there is a modified region of tubular epithelium called the macula densa. Cells in the macula densa respond to changes in the sodium chloride levels in the distal tubule of the nephron via the tubuloglomerular feedback (TGF) loop.

The macula densa's detection of elevated sodium chloride, which leads to an increase in GFR, is based on the concept of purinergic signalling. An increase in the salt concentration causes several cell signals to eventually cause the adjacent afferent arteriole to constrict. This decreases the amount of blood coming from the afferent arterioles to the glomerular capillaries, and therefore decreases the amount of fluid that goes from the glomerular capillaries into the Bowman's space (the glomerular filtration rate (GFR).

When there is a decrease in the sodium concentration, less sodium is reabsorbed in the macular densa cells. The cells increase the production of nitric oxide and Prostaglandins to vasodilate the afferent arterioles and increase renin release.

Clinical Significance

Excess secretion of renin by the juxtaglomerular cells can lead to excess activity of the renin–angiotensin system, hypertension and an increase in blood volume. This is not responsive to the usual treatment for essential hypertension, namely medications and lifestyle modification.

One cause of this can be increased renin production due to narrowing of the renal artery, or a tumour of juxtaglomerular cells that produces renin. These will lead to secondary hyperaldosteronism, which will cause hypertension, high blood sodium, low blood potassium, and metabolic alkalosis

**Question Four: Discuss the role of kidney in regulation of blood pressure**

The kidneys play a central role in the regulation of arterial blood pressure. A large body of experimental and physiological evidence indicates that renal control of extracellular volume and renal perfusion pressure are closely involved in maintaining the arterial circulation and blood pressure. Renal artery perfusion pressure directly regulates sodium excretion; a process known as pressure natriuresis, and influences the activity of various vasoactive systems such as the renin–angiotensin–aldosterone (RAS) system. Along with vessel morphology, blood viscosity is one of the key factors influencing resistance and hence blood pressure. A key modulator of blood viscosity is the renin-angiotensin system (RAS) or the renin-angiotensin-aldosterone system (RAAS), a hormone system that regulates blood pressure and water balance.

The blood pressure in the body depends upon:

• The force by which the heart pumps out blood from the ventricles of the heart - and this is dependent on how much the heart muscle gets stretched by the inflowing blood into the ventricles.

• The degree to which the arteries and arterioles constrict-- increases the resistance to blood flow, thus requiring a higher blood pressure.

• The volume of blood circulating round the body; if the volume is high, the ventricles get more filled, and the heart muscle gets more stretched.

The kidney influences blood pressure by:

• Causing the arteries and veins to constrict

• Increasing the circulating blood volume

Specialized cells called macula densa are located in a portion of the distal tubule located near and in the wall of the afferent arteriole. These cells sense the Na in the filtrate, while the arterial cells (juxtaglomerular cells) sense the blood pressure. When the blood pressure drops, the amount of filtered Na also drops. The arterial cells sense the drop in blood pressure, and the decrease in Na concentration is relayed to them by the macula densa cells. The juxtaglomerular cells then release an enzyme called renin.

Renin converts angiotensinogen (a peptide, or amino acid derivative) into angiotensin-1. Angiotensin-1 is thereafter converted to angiotensin-2 by an angiotensin-converting enzyme (ACE), found in the lungs. Angiotensin-2 causes blood vessels to contract -- the increased blood vessel constrictions elevate the blood pressure. When the volume of blood is low, arterial cells in the kidneys secrete renin directly into circulation. Plasma renin then carries out the conversion of angiotensinogen released by the liver to angiotensin-1. Angiotensin-1 is subsequently converted to angiotensin-2 by the enzyme angiotensin converting enzyme found in the lungs. Angiotensin-2m a potent vasoactive peptide causes blood vessels to constrict, resulting in increased blood pressure. Angiotensin-2 also stimulates the secretion of the hormone aldosterone from the adrenal cortex.

Aldosterone causes the tubules of the kidneys to increase the reabsorption of sodium and water into the blood. This increases the volume of fluid in the body, which also increases blood pressure. If the renin-angiotensin-aldosterone system is too active, blood pressure will be too high. Many drugs interrupt different steps in this system to lower blood pressure. These drugs are one of the main ways to control high blood pressure (hypertension), heart failure, kidney failure, and harmful effects of diabetes. It is believed that angiotensin-1 may have some minor activity, but angiotensin-2 is the major bioactive product. Angiotensin-2 has a variety of effects on the body: throughout the body, it is a potent vasoconstrictor of arterioles.

**Mechanisms of blood pressure control by the kidneys**

1. Intra-renal actions of the renin-angiotensin system in blood pressure control

The renin-angiotensin system (RAS) is a potent modulator of blood pressure, and dysregulation of the RAS results in hypertension. Pharmacological blockade of the RAS with renin inhibitors, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin receptor blockers effectively lowers blood pressure in a substantial proportion of patients with hypertension, reflecting the important role for RAS activation as a cause of human hypertension. While in rodents, deletion of RAS genes lowers blood pressure, overexpression causes hypertension.

While The distal tubule cells (macula densa) sense the Na in the filtrate, and the arterial cells (juxtaglomerular cells) sense the blood pressure. Studies have shown that chronic infusion of low doses of angiotensin II directly into the kidney caused hypertension with impaired natriuresis due to a shift of the pressure-natriuresis relationship. It is also believed that the existence of local and independent control of RAS activity within the kidney influencing sodium excretion and blood pressure regulation. In this hypothesis, increased circulating levels of angiotensin II are associated with accumulation of angiotensin peptides in the kidney, upregulated expression of angiotensinogen, the primary RAS substrate, in proximal tubule epithelium, and increased excretion of angiotensinogen and angiotensin peptides in urine. In this feed-forward pathway, angiotensin II acting via type 1 angiotensin (AT1) receptors in the kidney induces local activation of the RAS inside the kidney and increases generation of angiotensin II in the lumen of renal tubules, resulting in autocrine and paracrine stimulation of epithelial transporters.

Recent studies in support of this idea have verified the critical requirement of ACE within the kidney to fully manifest stimulation of sodium transporter expression, renal sodium reabsorption, and hypertension in the setting of RAS activation.

2. Novel Control Mechanisms and Sites of Action for Aldosterone in Hypertension

AT1 receptors in the zona glomerulosa of the adrenal gland stimulate aldosterone release, making aldosterone a downstream effector of the RAS. Activation of the mineralocorticoid receptor (MR) in aldosterone-sensitive nephron segments stimulates assembly and translocation of the subunits of the ENaC. Mutations in ENaC subunits that impair its degradation result in enhanced membrane density and open probability of the channels, resulting in Liddle’s syndrome, characterized by severe, early onset hypertension resembling hyper-aldosteronism, but with low levels of aldosterone. Similarly, activating mutations in the gene encoding the MR also cause hypertension that is exacerbated by steroid hormone alterations during pregnancy. These syndromes may highlight the capacity for dysregulation of the MR/ENaC signaling pathway in the kidney to promote hypertension.

Aldosterone, in addition to stimulation of sodium reabsorption, promotes secretion of potassium into urine. Shibata et al have shown in their studies that regulated phosphorylation of the MR modulates aldosterone responses in the kidney. They showed that phosphorylation of S843 on the MR prevents ligand binding. This form of the MR is present only in intercalated cells of the collecting duct of the kidney where its phosphorylation is differentially regulated by volume depletion and hyperkalemia. For example, in volume depletion, the MR in intercalated cells is dephosphorylated, resulting in potentiation of chloride and sodium reabsorption, allowing a distinct response to volume depletion. Although the MR is classically activated by aldosterone, recent studies suggest that the small GTPase Rac1 may promote hypertension through an MR-dependent pathway, even in the setting of suppressed aldosterone levels.

3) Salt Homeostasis

Salt sensitivity, defined as an exaggerated change in blood pressure in response to extremes in dietary salt intake, is relatively common and is associated with an increased risk for the development of hypertension. Classic Guytonian models suggest that a defect in sodium excretion by the kidney is the basis for salt sensitivity, with impaired elimination of sodium during high-salt feeding leading directly to expanded extracellular fluid volume, which promotes increased blood pressure. This model presumes that the two major components of extracellular volume within the intravascular and interstitial spaces are in equilibrium. As such, accumulation of sodium would be accompanied by commensurate retention of water to maintain iso-osmolality and would thereby proportionally expand the intravascular volume.

However, studies by Titze et al. recently indicated that sodium handling is more complex than this classical two-compartment model; the interstitium of the skin may act as a sodium reservoir, buffering the impact of sodium accumulation on intravascular volume and blood pressure. During high-salt feeding, sodium accumulates in the subdermal interstitium at hypertonic concentrations in complexes with proteoglycans. Macrophages infiltrating the interstitial space sense hypertonicity caused by this accumulation of sodium in excess of water, triggering expression of TonEBP, a transcription factor regulating the expression of osmo-protective genes. One of the genes induced downstream of TonEBP is vascular endothelial Growth Factor-C (VEGF-C), a potent inducer of lymph angiogenesis.

In response to high-salt feeding, Titze’s group found robust lymphatic vessel hyperplasia in the dermal interstitium. Depletion of macrophages, cell-specific deletion of TonEBP from macrophages, or specific blockade of VEGF-C prevented hyperplasia of lymphatic vessels and enhanced the level of sodium-dependent hypertension demonstrating that this pathway has a key role in the extrarenal control of sodium and fluid volumes. Elevated plasma level of VEGF-C in patients with refractory hypertension was observed, indicating that this system might be perturbed in the human disorder. However, pre-clinical models predict that reduced levels of VEGF-C would promote hypertension. Nonetheless, chronic hypertension in humans is a complex disorder; it is possible that the observed elevation in VEGF-C levels may reflect tissue resistance to VEGF-C or even a compensatory response.

Clinical Significance

The kidney remains a major site for hypertensive target organ damage which is second only to diabetic nephropathy as a primary cause for end-stage renal disease (ESRD). Moreover, the presence of chronic kidney disease (CKD), including that caused by hypertension, has been shown to be a strong independent risk factor for adverse cardiovascular outcomes. Nevertheless, major aspects of clinical hypertensive renal disease remain poorly understood such as the marked differences in individual susceptibility to hypertensive renal damage and the apparent variable reno-protective effectiveness of antihypertensive classes.

Studies have revealed that time-varying SBP was associated with incident CKD, with a steady increase in risk of incident CKD above an SBP of 120 mmHg. Time-weighted SBP was associated with a more rapid decline of kidney function. Diabetes was the strongest predictor of incident CKD, and more rapid decline of kidney function and worse glycemic control were associated with greater risk, thereby supporting the role of BP and other traditional risk factors like diabetes in the initiation and progression of kidney function decline in hypertensive patients with normal kidney function at baseline.

**Question Five: Discuss the role of kidney in calcium homeostasis**

About 50% of plasma calcium (ionized and complexed form; ultrafilterable 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. PTH 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/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 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.

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 paracellular Ca2+ channel in the PT6). 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 paracellular 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 calcium-binding 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.