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PHS 303 Assignment; - Renal Physiology.

Course Title: - Renal Physiology Body Fluid and Temperature Regulation.

1) Role of Kidney in Glucose Homeostasis.

The human 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
iii) Reabsorption into the circulation of glucose from glomerular filtrate to conserve glucose carbon.

Plasma glucose concentrations are determined by the relative rates of glucose entry into, and removal from, the circulation. Normally, despite wide daily fluctuations in the rate of delivery of glucose into the circulation (e.g. meal ingestion) and in the demands of tissues for glucose (e.g. during exercise), plasma levels are maintained within a relatively narrow range throughout the day.

Insulin suppresses glucose release in both the liver and kidney by direct enzyme activation/deactivation, as well as by reducing the availability of gluconeogenic substrates and actions on gluconeogenic activators. Glucagon has no effect on the kidney, but increases both gluconeogenesis and glycogenolysis in the liver. Catecholamines have multiple acute actions, including stimulation of renal glucose release, inhibition of insulin secretion, stimulation of

glucagon secretion, and increases in gluconeogenic substrate supply, stimulation of lipolysis and reduced tissue glucose uptake.

The kidney is unable to release glucose through glycogenolysis because it contains very little glycogen and those renal cells that are able to synthesize glycogen lack the enzyme glucose-6-phosphatase and therefore cannot release glucose. In humans, only the liver and kidney contain significant amounts of the enzyme glucose-6-phosphatase and therefore are the only organs that are able to perform gluconeogenesis. Research over the last 15–20 years has established that the human liver and kidneys provide about equal amounts of glucose via gluconeogenesis in the post-absorptive state. Consequently, after an overnight fast, 75–80% of glucose released into the circulation derives from the liver and the remaining 20–25% derives from the kidneys. As the duration of fasting increases, glycogen stores in the liver become further depleted until, after 48 h, virtually all the glucose released into the circulation is derived from gluconeogenesis. Consequently, as the length of fast increases, the proportion of overall glucose release accounted for by renal gluconeogenesis increases.

Renal glucose utilization

In the post-absorptive setting after an overnight fast, the kidneys utilize 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, not carbon dioxide (CO_2) and water. 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 reabsorption

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. Normally, approximately 180l of plasma are filtered by the kidneys each day. As the average plasma glucose concentration throughout a 24-h period is ∼5.5 mmol/l (100 mg/dl), ∼180g 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 15–55g glucose via gluconeogenesis and metabolize 25–35g 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 (Km ∼0.2 mmol/l; Vmax ∼10 nmol/ (min mg) protein; 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. 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.

2) <u>Process of Micturition.</u>

Micturition is the process by which the urinary bladder empties when it becomes filled. This involves two main steps: -

a) the bladder fills progressively until the tension in its walls rises above a threshold level. This is otherwise known as the **Resting or Filling stage.** This elicits the second step;
b) which is a nervous reflex called the micturition reflex that empties the bladder or, if this fails, at least causes a conscious desire to urinate. This is otherwise known as the **Voiding stage.**

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.

Filling of the Bladder.

The walls of the ureters contain smooth muscle arranged in spiral, longitudinal, and circular bundles, but distinct layers of muscle are not seen. Regular peristaltic contractions occurring one to five times per minute move the urine from the renal pelvis to the bladder, where it enters in spurts synchronous with each peristaltic wave. The ureters pass obliquely through the bladder wall and, although there are no ureteral sphincters as such, the oblique passage tends to keep the ureters closed except during peristaltic waves, preventing reflux of urine from the bladder.

Emptying of the Bladder.

The smooth muscle of the bladder, like that of the ureters, is arranged in spiral, longitudinal, and circular bundles. Contraction of the circular muscle, which is called the detrusor muscle, is mainly responsible for emptying the bladder during urination (micturition). Muscle bundles pass on either side of the urethra, and these fibres are sometimes called the internal urethral sphincter, although they do not encircle the urethra. Farther along the urethra is a sphincter of skeletal muscle, the sphincter of the membranous urethra (external urethral sphincter). The bladder epithelium is made up of a superficial layer of flat cells and a deep layer of cuboidal cells. Micturition is fundamentally a spinal reflex facilitated and inhibited by higher brain centers and, like defecation, subject to voluntary facilitation and inhibition. Urine enters the bladder without producing much increase in intravesical pressure until the viscus is well filled. In addition, like

other types of smooth muscle, the bladder muscle has the property of plasticity; when it is stretched, the tension initially produced is not maintained. The first urge to void is felt at a bladder volume of about 150 mL, and a marked sense of fullness at about 400 mL.

During micturition, the perineal muscles and external urethral sphincter are relaxed; the detrusor muscle contracts; and urine passes out through the urethra. The bands of smooth muscle on either side of the urethra apparently play no role in micturition, and their main function is believed to be the prevention of reflux of semen into the bladder during ejaculation. The mechanism by which voluntary urination is initiated remains unsettled. One of the initial events is relaxation of the muscles of the pelvic floor, and this may cause a sufficient downward tug on the detrusor muscle to initiate its contraction. The perineal muscles and external sphincter can be contracted voluntarily, preventing urine from passing down the urethra or interrupting the flow once urination has begun. It is through the learned ability to maintain the external sphincter in a contracted state that adults are able to delay urination until the opportunity to void presents itself. After urination, the female urethra empties by gravity. Urine remaining in the urethra of the male is expelled by several contractions of the bulbocavernosus muscle.

Reflex Control.

The bladder smooth muscle has some inherent contractile activity; however, when its nerve supply is intact, stretch receptors in the bladder wall initiate a reflex contraction that has a lower threshold than the inherent contractile response of the muscle. Fibers in the pelvic nerves are the afferent limb of the voiding reflex, and the parasympathetic fibers to the bladder that constitute the efferent limb also travel in these nerves. The reflex is integrated in the sacral portion of the spinal cord. In the adult,

the volume of urine in the bladder that normally initiates a reflex contraction is about 300–400 mL. The sympathetic nerves to the bladder play no part in micturition, but they do mediate the contraction of the bladder muscle that prevents semen from entering the bladder during ejaculation. The stretch receptors in the bladder wall have no small motor nerve system. However, the threshold for the voiding reflex, like the stretch reflexes, is adjusted by the activity of facilitatory and inhibitory centers in the brainstem.

There is a facilitatory area in the pontine region and an inhibitory area in the midbrain. After transection of the brain stem just above the pons, the threshold is lowered and less bladder filling is required to trigger it, whereas after transection at the top of the midbrain, the threshold for the reflex is essentially normal. There is another facilitatory area in the posterior hypothalamus. Humans with lesions in the superior frontal gyrus have a reduced desire to urinate and difficulty in stopping micturition once it has commenced. The bladder can be made to contract by voluntary facilitation of the spinal voiding reflex when it contains only a few millilitres of urine. Voluntary contraction of the abdominal muscles aids the expulsion of urine by increasing the intra-abdominal pressure, but voiding can be initiated without straining even when the bladder is nearly empty.

3) Juxtaglomerular Apparatus.

Juxtaglomerular apparatus is a specialized organ situated near the glomerulus of each nephron (juxta = near). It is formed by three different structures: -

i) Macula densa
ii) Extraglomerular mesangial cells
iii) Juxtaglomerular cells.

i) Macula Densa: -

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. Macula densa is formed by tightly packed cuboidal epithelial cells.

ii) Extraglomerular mesangial cells: -

These 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.

Glomerular Mesangial Cells: -

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. Glomerular mesangial cells are phagocytic in nature. These cells also secrete glomerular interstitial matrix, prostaglandins and cytokines.

iii) Juxtaglomerular cells: -

These 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. Juxtaglomerular cells are also called granular cells because of the presence of secretary granules in their cytoplasm.

The primary function of juxtaglomerular apparatus is the secretion of hormones. It also regulates the glomerular blood flow and glomerular filtration rate. The hormones secreted by juxtaglomerular apparatus are; Renin and Prostaglandin.

4) 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-2 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.

5) Role of Kidney in Calcium Homeostasis.

Because calcium is both filtered and reabsorbed in the kidneys but not secreted, the rate of renal calcium excretion is calculated as Renal calcium excretion = Calcium filtered - Calcium reabsorbed. Only about 50 per cent of the plasma calcium is ionized, with the remainder being bound to the plasma proteins or complexed with anions such as phosphate. Therefore, only about 50 per cent of the plasma calcium can be filtered at the glomerulus.

Normally, about 99 per cent of the filtered calcium is reabsorbed by the tubules, with only about 1 per cent of the filtered calcium being excreted. About 65 per cent of the filtered calcium is reabsorbed in the proximal tubule, 25 to 30 per cent is reabsorbed in the loop of Henle, and 4 to 9 per cent is reabsorbed in the distal and collecting tubules. This pattern of reabsorption is similar to that for sodium. As is true with the other ions, calcium excretion is adjusted to meet the body's needs. With an increase in calcium intake, there is also 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 as a result of

enhanced tubular reabsorption. One of the primary controllers of renal tubular calcium reabsorption is Parathyroid hormone.

With increased levels of Parathyroid hormone, there is increased calcium reabsorption in the thick ascending loops of Henle and distal tubules, which reduces urinary excretion of calcium. Conversely, reduction of Parathyroid hormone promotes calcium excretion by decreasing reabsorption in the loops of Henle and distal tubules. In the proximal tubule, calcium reabsorption usually parallels sodium and water reabsorption. Therefore, in instances of extracellular volume expansion or increased arterial pressure—both of which decrease proximal sodium and water reabsorption—there is also reduction in calcium reabsorption and, consequently, increased urinary excretion of calcium. Conversely, with extracellular volume contraction or decreased blood pressure, calcium excretion decreases primarily because of increased proximal tubular reabsorption. Another factor that influences calcium reabsorption is the plasma concentration of phosphate. An increase in plasma phosphate stimulate Parathyroid hormone, which increases calcium reabsorption by the renal tubules, thereby reducing calcium excretion.

The opposite occurs with reduction in plasma phosphate concentration. Calcium reabsorption is also stimulated by metabolic acidosis and inhibited by metabolic alkalosis. Most of the effect of hydrogen ion concentration on calcium excretion results from changes in calcium reabsorption in the distal tubule.