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RENAL PHYSIOLOGY

**Role of kidney in glucose homeostasis**

SGLT2 is a high‐capacity, low‐affinity glucose transporter (GLUT) located in the early convoluted segment (S1) of the proximal tubule, where luminal glucose is abundant . The SGLT2 transporter mediates 90% of renal glucose reabsorption by coupling glucose transport to the electrochemical sodium gradient . First, sodium is absorbed across the luminal cell membrane, creating an energy gradient that permits glucose to passively enter the cell. Then, an adenosine triphosphatase (ATPase)‐mediated sodium–potassium pump returns the sodium to the bloodstream. This exchange alters the concentration gradient within the cell, and glucose diffuses to the basolateral GLUT2, through which it passes back into the bloodstream .

The other 10% of renal glucose reabsorption occurs through SGLT1, a high‐affinity, low‐capacity transport protein that is found in the more distal, straight section of the proximal tubule , where there is less luminal glucose . SGLT1 also resides in the intestine, where it is responsible for absorption of dietary glucose and galactose .Because SGLT1 resides in intestinal as well as renal tissues, and because it is not specific for glucose alone, it is not considered a viable target for therapeutic intervention. Inhibition of this transporter has the potential to cause osmotic diarrhoea and malabsorption. However, as long as clinically significant gastrointestinal side effects are not observed, combined SGLT2/SGLT1 inhibition remains a therapeutic option.

In the kidney, the amount of glucose reabsorbed through the SGLT1 and SGLT2 transporters is equal to the amount of glucose that is filtered by the glomerulus. Glucose reabsorption by the proximal tubule increases linearly with increasing glucose concentration, approximately 11 mmol/l . At this concentration, the glucose transport system becomes saturated and all the filtered glucose in excess of this threshold is excreted in the urine. This threshold varies from nephron to nephron, because of both anatomical and physiologic heterogeneity between nephrons, and this results in slight differences in glucose reabsorption levels between individual renal tubules. Thus, the actual threshold at which glucose starts to appear in the urine is slightly below the maximum of 11 mmol/l and occurs gradually in a curve linear slope that begins at approximately 10 mmol/l.

**Process of micturition**

Micturition or urination is the process of expelling urine from the bladder. This act is also known as voiding of the bladder. The excretory system in humans includes a pair of kidneys, two ureters, a urinary bladder and a urethra. 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. When bladder volume reaches about 150 mL, an urge to void is sensed but is easily overridden. Voluntary control of urination relies on consciously preventing relaxation of the external urethral sphincter to maintain urinary continence. As the bladder fills, subsequent urges become harder to ignore. The urinary bladder can store around 350-400ml of urine but at this volume subsequent urges become harder to ignore. Ultimately, voluntary constraint fails with resulting incontinence and the urine is expelled.

The opening, described as the neck of the bladder, between the bladder and the urethra, is closed by two rings of muscle - the internal and external sphincters. The internal sphincter contains smooth muscle fibres and the normal muscle tone of these fibres keeps it contracted; it is therefore not under voluntary control. The external sphincter is formed of a circular band of skeletal muscle which is supplied by the pudendal nerve and is under voluntary control. These fibres remain contracted, as a result of central nervous system stimulation, except during micturition when they relax. Normal micturition is a result of the stretch receptors in the bladder wall that transmit nerve impulses to the sacral region of the spinal cord to generate a spinal reflex. The resulting parasympathetic neural outflow causes contraction of the detrusor muscle and relaxation of the involuntary internal urethral sphincter. At the same time, the spinal cord inhibits somatic motor neurons, resulting in the relaxation of the skeletal muscle of the external urethral sphincter.

Micturition, or urination, occurs involuntarily in infants and young children until the age of 3 to 5 years, after which it is regulated voluntarily. The neural circuitry that controls this process is complex and highly distributed: it involves pathways at many levels of the brain, the spinal cord and the peripheral nervous system and is mediated by multiple neurotransmitters. Diseases or injuries of the nervous system in adults can cause the re-emergence of involuntary or reflex micturition, leading to urinary incontinence. This is a major health problem, especially in those with neurological impairment.

**Juxtaglomerular apparatus**

The juxtaglomerular apparatus is part of the kidney nephron that synthesize, store, and secrete the enzyme rennin, is located between the afferent arteriole and the returning distal convoluted tubule of the same nephron.

The three components of the JGA are the following:

(1) the juxtaglomerular cells of the afferent arteriole, synthesize and store renin, which is secreted in response to specific stimuli (e.g., low blood flow, decreased NaCl delivery). The juxtaglomerular cells could be considered the “effector arm” of the renin-angiotensin-aldosterone axis.

(2) the macula densa, a region of the distal convoluted tubule characterized by tubular epithelial cells which are more densely-packed than in other regions of the nephron (and thereby leading to its characteristic appearance on light microscopy). The macula densa can be considered the “sensory arm” of the renin-angiotensin-aldosterone axis in that these are the cells which sense decreased Na Cl delivery which determines downstream function. They are also involved in the mechanism of tubuloglomerular feedback.

(3) mesangial cells, which form connections via actin and microtubules which allow for selective vasoconstriction/vasodilation of the renal afferent and efferent arterioles with mesangial cell contraction.

**Role of kidney in regulation of blood pressure**

The kidneys play a central role in the regulation of arterial blood pressure. A key modulator of blood viscosity is the renin-angiotensin system (RAS) it’s one of the major control systems for blood pressure and fluid balance. The major biologically active hormone generated by this system, angiotensin (Ang) II, is produced by sequential cleavage of peptides derived from the substrate molecule angiotensinogen (Agt).

Ang II increases arterial pressure via two principal effects. The first, vasoconstriction, occurs very rapidly, within seconds, and very intensely in the arterioles and to a considerably lesser extent in the veins. The second is the effect on the kidneys to decrease the excretion of both salt and water. This increases the extracellular fluid volume, which then increases arterial pressure slowly over a period of hours and days. This long-term effect, acting through the extracellular fluid volume mechanism, is even more powerful than the acute vasoconstrictor mechanism in increasing blood pressure. Ang II causes the kidneys to retain salt and water through extrarenal and intrarenal mechanisms. Ang II increases sympathetic nerve stimulation, which increases renal tubular sodium reabsorption directly or indirectly through renal vasoconstriction. Moreover, Ang II stimulates the synthesis and secretion of aldosterone from the adrenal cortex, and aldosterone in turn increases salt and water reabsorption by the distal tubule. Within the kidney, Ang II increases predominantly proximal tubular sodium reabsorption. It also induces renal microvascular constriction, in particular of the efferent arterioles. This helps maintaining the glomerular filtration rate and tends to increase sodium reabsorption by altering peritubular capillary physical forces.During hypovolemia (for example, hemorrhagic shock) and in sodium-deficient states, intrarenal Ang II levels are elevated and, in turn, increase both renal sodium and water reabsorption, thereby playing an important physiological role in maintaining circulating volume and blood pressure.

**Role of Kidney in Calcium homeostasis**

Ca2+ homeostasis is achieved through a fine balance among three main organs: the intestine, the kidney, and bone. Blood levels of Ca2+ are accurately tuned through the Ca2+ sensing receptors and regulated by several hormones, including parathyroid hormone (PTH), active vitamin D, and calcitonin**.**

The kidneys play an important role in maintaining healthy bone mass and structure by balancing phosphorus and calcium levels in the blood. Healthy kidneys activate a form of vitamin D that a person consumes in food, turning it into calcitriol, the active form of the vitamin. Calcitriol helps the kidneys maintain blood calcium levels and promotes the formation of bone.