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18/MHS07/019
PHARMACOLOGY
PHS 212
Assignment
Discuss the renal handling of glucose and electrolytes?

•Renal handling of Glucose

Glucose is completely reabsorbed in the proximal convoluted tubule. It is transported by secondary active transport (sodium cotransport) mechanism. Glucose and sodium bind to a common carrier protein in the luminal membrane of tubular epithelium and enter the cell. The carrier protein is called sodium-dependant glucose cotransporter 2 (SGLT2). From tubular cell glucose is transported into medullary interstitium by another carrier protein called glucose transporter 2 (GLUT2).

Tubular maximum for glucose (TmG)

In adult male, TmG is 375 mg/minute and in adult females it about 300 mg/minute.

Renal threshold for glucose

Renal threshold for glucose is 180 mg/dL in venous blood. When the blood level reaches 180 mg/dL glucose is not reabsorbed completely and appears in urine.

Splay

Splay means deviation. With normal GFR of 125 mL/ minute and TmG of 375 mg/minute in an adult male the predicted (expected) renal threshold for glucose should be 300 mg/dL. But actually it is only 180 mg/dL.

When the renal threshold curves are drawn by using these values, the actual curve deviates from the 'should be' or predicted or ideal curve. This type of deviation is called splay. Splay is because of the fact that all the nephrons do not have the same filtering and reabsorbing capacities.

•Renal handling of Sodium

From the glomerular filtrate, 99% of sodium is reabsorbed. Two thirds of sodium is reabsorbed in proximal convoluted tubule and remaining one third in other segments (except descending limb) and collecting duct.

Sodium reabsorption occurs in three steps:

1. Transport from lumen of renal tubules into the tubular epithelial cells
2. Transport from tubular cells into the interstitial fluid
3. Transport from interstitial fluid to the blood.

1. Transport from Lumen of Renal Tubules into the Tubular Epithelial Cells

Active reabsorption of sodium ions from lumen into the tubular cells occurs by two ways:

i. In exchange for hydrogen ion by antiport (sodium counterport protein) – in proximal convoluted tubules

ii. Along with other substances like glucose and amino acids by symport (sodium co transport protein) – in other segments and collecting duct.

It is believed that some amount of sodium diffuses along the electrochemical gradient from lumen into tubular cell across the luminar membrane. The electro chemical gradient is developed by sodium potassium pump (see below).

2. Transport from Tubular Cells into the Interstitial Fluid

Sodium is pumped outside the cells by sodium potassium pump. This pump moves three sodium

ions from the cell into interstitium and two potassium ions from interstitium into the cell.

Tubular epithelial cells are connected with their neighboring cells by tight junctions at their apical luminal edges. But, beyond the tight junction, a small space is left between the adjoining cells along their lateral borders. This space is called lateral intercellular space. The interstitium extends into this space.

Most of the sodium ions are pumped into the lateral intercellular space by sodium potassium pump. The rest of the sodium ions are pumped into the interstitial by the sodium potassium pump situated at the basal part of the cell membrane.

(Transport of sodium out of the tubular cell by sodium potassium pump, decreases the sodium concentration within the cell. This develops an electrochemical gradient between the lumen and tubular cell resulting in diffusion of sodium into the cell).

3. Transport from Interstitial Fluid to the Blood

From the interstitial fluid, sodium ions enter the peritubular capillaries by concentration gradient. In the distal convoluted tubule, the sodium reabsorption is stimulated by the hormone aldosterone secreted by adrenal cortex.

•Renal handling of Water

Reabsorption of water occurs from proximal and distal convoluted tubules and in collecting duct. Reabsorption of water from proximal convoluted tubule.

Obligatory water reabsorption

Obligatory reabsorption is the type of water reabsorption in proximal convoluted tubule, which is secondary (obligatory) to sodium reabsorption. When sodium is reabsorbed from the tubule, the osmotic pressure decreases. It causes osmosis of water from renal tubule.

Reabsorption of water from distal convoluted tubule and collecting duct – **Facultative water reabsorption**

Facultative reabsorption is the type of water reabsorption in distal convoluted tubule and collecting duct that occurs by the activity of antidiuretic hormone (ADH). Normally, the distal convoluted tubule and the collecting duct are not permeable to water. But in the presence of ADH, these segments become permeable to water, so it is reabsorbed.

Mechanism of action of ADH – Aquaporins

Antidiuretic hormone increases water reabsorption in distal convoluted tubules and collecting ducts by stimulating the water channels called aquaporins. ADH combines with vasopressin (V2) receptors in the tubular epithelial membrane and activates adenyl cyclase, to form cyclic AMP. This cyclic AMP activates the aquaporins, which increase the water reabsorption.

Aquaporins (AQP) are the membrane proteins, which function as water channels. Though about 10 aquaporins are identified in mammals only 5 are found in humans. Aquaporin 1, 2 and 3 are present in renal tubules. Aquaporin 4 is present in brain and aquaporin 5 is found in salivary glands. Aquaporin 2 forms the water channels in renal tubules.

•Renal handling of Bicarbonates

Bicarbonate is reabsorbed actively, mostly in proximal tubule. It is reabsorbed in the form of carbon dioxide.

Bicarbonate is mostly present as sodium bicarbonate in the filtrate. Sodium bicarbonate dissociates into sodium and bicarbonate ions in the tubular lumen. Sodium diffuses into tubular cell

in exchange of hydrogen. Bicarbonate combines with hydrogen to form carbonic acid. Carbonic acid dissociates into carbon dioxide and water in the presence of carbonic anhydrase. Carbon dioxide and water enter the tubular cell.

In the tubular cells, carbon dioxide combines with water to form carbonic acid. It immediately dissociates into hydrogen and bicarbonate. Bicarbonate from the tubular cell enters the interstitium. There it combines with sodium to form sodium bicarbonate.

•Renal handling of Calcium

60% of the filtered calcium is reabsorbed in the proximal tubule with the paracellular absorption of water (solvent drag). Additionally, there are active transport mechanisms.

•Renal handling of Phosphate

Phosphate is completely filtered, 80–90% of the phosphate are reabsorbed in the proximal tubule. With high phosphate concentrations in serum, a saturation of the phosphate reabsorption is reached and phosphate is excreted till the normalization of the phosphate concentration. An increased phosphate concentration is the stimulus for the parathyroid hormone release and leads to phosphate excretion, calcium phosphate deposition into the bone and lowers the serum calcium.

Discuss the physiology of micturition?

• PHYSIOLOGY OF MICTURITION

Micturition is a process by which urine is voided from the urinary bladder. It is a reflex process. However, in grown up children and adults, it can be controlled voluntarily to some extent. The functional anatomy and nerve supply of urinary bladder are essential for the process of micturition.

FUNCTIONAL ANATOMY OF URINARY BLADDER AND URETHRA

URINARY BLADDER

Urinary bladder is a triangular hollow organ located in lower abdomen. It consists of a body and neck. Wall of the bladder is formed by smooth muscle. It consists of three ill-defined layers of muscle fibers called detrusor muscle, viz. the inner longitudinal layer, middle circular layer and outer longitudinal layer. Inner surface of urinary bladder is lined by mucus membrane. In empty bladder, the mucosa falls into many folds called rugae.

At the posterior surface of the bladder wall, there is a triangular area called trigone. At the upper angles of this trigone, two ureters enter the bladder. Lower part of the bladder is narrow and forms the neck. It opens into urethra via internal urethral sphincter.

URETHRA

Male urethra has both urinary function and reproductive function. It carries urine and semen. Female urethra has only urinary function and it carries only urine. So, male urethra is structurally different from female urethra.

Male Urethra

Male urethra is about 20 cm long. After origin from bladder it traverses the prostate gland, which lies below the bladder and then runs through the penis.

Throughout its length, the urethra has mucus glands called glands of Littre.

Male urethra is divided into three parts:

1. Prostatic urethra

2. Membranous urethra
3. Spongy urethra.

1. Prostatic urethra

Prostatic urethra is 3 cm long and it runs through prostate gland. The prostatic fluid is emptied into this part of urethra through prostatic sinuses. Sperms from vas deferens and the fluid from seminal vesicles are also emptied into prostatic urethra via ejaculatory ducts.

Part of the urethra after taking origin from neck of bladder before entering the prostate gland is known as preprostatic urethra. Its length is about 0.5 to 1.5 cm. This part of urethra is considered as part of prostatic urethra.

2. Membranous urethra

Membranous urethra is about 1 to 2 cm long. It runs from base of the prostate gland through urogenital diaphragm up to the bulb of urethra.

3. Spongy urethra

Spongy urethra is also known as cavernous urethra and its length is about 15 cm. Spongy urethra is surrounded by corpus spongiosum of penis. It is divided into a proximal bulbar urethra and a distal penil urethra. Penile urethra is narrow with a length of about 6 cm. It ends with external urethral meatus or orifice, which is located at the end of penis.

The bilateral bulbourethral glands open into spongy urethra. Bulbourethral glands are also called Cowper glands.

Female Urethra

Female urethra is narrower and shorter than male urethra. It is about 3.5 to 4 cm long. After origin from bladder it traverses through urogenital diaphragm and runs along anterior wall of vagina. Then it terminates at external orifice of urethra, which is located between clitoris and vaginal opening.

URETHRAL SPHINCTERS

There are two urethral sphincters in urinary tract:

1. Internal urethral sphincter
2. External urethral sphincter.

1. Internal Urethral sphincter

This sphincter is situated between neck of the bladder and upper end of urethra. It is made up of smooth muscle fibers and formed by thickening of detrusor muscle. It is innervated by autonomic nerve fibers. This sphincter closes the urethra when bladder is emptied.

2. External Urethral sphincter

External sphincter is located in the urogenital diaphragm. This sphincter is made up of circular skeletal muscle fibers, which are innervated by somatic nerve fibers.

NERVE SUPPLY TO URINARY BLADDER AND SPHINCTERS

Urinary bladder and the internal sphincter are supplied by sympathetic and parasympathetic divisions of auto nomic nervous system where as, the external sphincter is supplied by the somatic nerve fibers.

SYMPATHETIC NERVE SUPPLY

Preganglionic fibers of sympathetic nerve arise from first two lumbar segments (L1 and L2) of spinal cord. After leaving spinal cord, the fibers pass through lateral sympathetic chain without any synapse in the sympathetic ganglia and finally terminate in hypogastric ganglion. The postganglionic fibers arising from this ganglion form the hypogastric nerve, which supplies the detrusor muscle and internal sphincter.

Function of Sympathetic Nerve

The stimulation of sympathetic (hypogastric) nerve causes relaxation of detrusor muscle and constriction of the internal sphincter. It results in filling of urinary
bladder and so, the sympathetic nerve is called nerve of filling.

PARASYMPATHETIC NERVE SUPPLY

Preganglionic fibers of parasympathetic nerve form the pelvic nerve or nervus erigens. Pelvic nerve fibers arise from second, third and fourth sacral segments (S1, S2 and S3) of spinal cord. These fibers run through hypogastric ganglion and synapse with postganglionic neurons situated in close relation to urinary bladder and internal sphincter.

Function of Parasympathetic Nerve

Stimulation of parasympathetic (pelvic) nerve causes contraction of detrusor muscle and relaxation of the internal sphincter leading to emptying of urinary bladder. So, parasympathetic nerve is called the nerve of emptying or nerve of micturition.

Pelvic nerve has also the sensory fibers, which carry impulses from stretch receptors present on the wall of the urinary bladder and urethra to the central nervous system. **SOMATIC NERVE SUPPLY**

External sphincter is innervated by the somatic nerve called pudendal nerve. It arises from second, third and fourth sacral segments of the spinal cord.

Function of Pudendal Nerve

Pudendal nerve maintains the tonic contraction of the skeletal muscle fibers of the external sphincter and keeps the external sphincter constricted always.

During micturition, this nerve is inhibited. It causes relaxation of external sphincter leading to voiding of urine. Thus, the pudendal nerve is responsible for voluntary control of micturition.

FILLING OF URINARY BLADDER

PROCESS OF FILLING

Urine is continuously formed by nephrons and it flows into urinary bladder drop by drop through ureters. When urine collects in the pelvis of ureter, the contraction sets up in pelvis. This contraction is transmitted through rest of the ureter in the form of peristaltic wave up to trigone of the urinary bladder. Peristaltic wave usually travels at a velocity of 3 cm/second. It develops at a frequency of 1 to 5 per minute. The peristaltic wave moves the urine into the bladder.

After leaving the kidney, the direction of the ureter is initially downward and outward. Then, it turns horizontally before entering the bladder. At the entrance of ureters into urinary bladder, a valvular arrangement is present. When peristaltic wave pushes the urine towards bladder, this valve opens towards the bladder. The position of ureter and the valvular arrangement at the end of ureter prevent the back flow of urine from bladder into the ureter when the detrusor muscle contracts. Thus, urine is collected in bladder drop by drop.

A reasonable volume of urine can be stored in urinary bladder without any discomfort and

without much increase in pressure inside the bladder (intravesical pressure). It is due to the adaptation of detrusor muscle. This can be explained by cystometrogram.

CYSTOMETROGRAM

Definition

Cystometry is the technique used to study the relationship between intravesical pressure and volume of urine in the bladder. Cystometrogram is the graphical registration (recording) of pressure changes in urinary bladder in relation to volume of urine collected in it.

Method of Recording Cystometrogram

A double lumen catheter is introduced into the urinary bladder. One of the lumen is used to infuse fluid into the bladder and the other one is used to record the pressure changes by connecting it to a suitable recording instrument.

First, the bladder is emptied completely. Then, a known quantity of fluid is introduced into the bladder at regular intervals. The intravesical pressure developed by the fluid is recorded continuously.

MICTURITION REFLEX

Micturition reflex is the reflex by which micturition occurs. This reflex is elicited by the stimulation of stretch receptors situated on the wall of urinary bladder and urethra. When about 300 to 400 mL of urine is collected in the bladder, intravesical pressure increases. This stretches the wall of bladder resulting in stimulation of stretch receptors and generation of sensory impulses.

Pathway for Micturition Reflex

Sensory (afferent) impulses from the receptors reach the sacral segments of spinal cord via the sensory fibers of pelvic (parasympathetic) nerve. Motor (efferent) impulses produced in spinal cord, travel through motor fibers of pelvic nerve towards bladder and internal sphincter. Motor impulses cause contraction of detrusor muscle and relaxation of internal sphincter so that, urine enters the urethra from the bladder.

Once urine enters urethra, the stretch receptors in the urethra are stimulated and send afferent impulses to spinal cord via pelvic nerve fibers. Now the impulses generated from spinal centers inhibit pudendal nerve. So, the external sphincter relaxes and micturition occurs.

Once a micturition reflex begins, it is self-regenerative, i.e. the initial contraction of bladder further activates the receptors to cause still further increase in sensory impulses from the bladder and urethra. These impulses, in turn cause further increase in reflex contraction of bladder. The cycle continues repeatedly until the force of contraction of bladder reaches the maximum and the urine is voided out completely.

During micturition, the flow of urine is facilitated by the increase in the abdominal pressure due to the voluntary contraction of abdominal muscles.

Higher Centers for Micturition

Spinal centers for micturition are present in sacral and lumbar segments. But, these spinal centers are regulated by higher centers. The higher centers, which control micturition are of two types, inhibitory centers and facilitatory centers.

Inhibitory centers for micturition

Centers in midbrain and cerebral cortex inhibit the micturition by suppressing spinal micturition centers.

Facilitatory centers for micturition

Centers in pons facilitate micturition via spinal centers. Some centers in cerebral cortex also facilitate micturition.

ABNORMALITIES OF MICTURITION

•ATONIC BLADDER – EFFECT OF DESTRUCTION OF SENSORY NERVE FIBERS

Atonic bladder is the urinary bladder with loss of tone in detrusor muscle. It is also called flaccid neurogenic bladder or hypoactive neurogenic bladder. It is caused by destruction of sensory (pelvic) nerve fibers of urinary bladder.

Due to the destruction of sensory nerve fibers, the bladder is filled without any stretch signals to spinal cord. Due to the absence of stretch signals, detrusor muscle
loses the tone and becomes flaccid. So the bladder is completely filled with urine without any micturition.

Now, urine overflows in drops as and when it enters the bladder. It is called overflow incontinence or overflow dribbling.

Conditions of Destruction of Sensory Nerve Fibers

1.Spinal injury: During the first stage (stage of spinal shock) after injury to sacral segments of spinal cord (Chapter 143) the bladder becomes atonic

2.Syphilis: Syphilis results in the degenerative nervous disorder called tabes dorsalis, which is characterized by the degeneration of dorsal (sensory) nerve roots .

Degeneration of sensory nerve roots of sacral region develops atonic bladder. The atonic bladder in tabes dorsalis is called tabetic bladder.

•AUTOMATIC BLADDER

Automatic bladder is the urinary bladder characterized by hyperactive micturition reflex with loss of voluntary control. So, even a small amount of urine collected in the bladder elicits the micturition reflex resulting in emptying of bladder.

This occurs during the second stage (stage of recovery) after complete transection of spinal cord above the sacral segments.

During the first stage (stage of spinal shock) after complete transection of spinal cord above sacral segments, the urinary bladder loses the tone and becomes atonic resulting in overflow incontinence.

During the second stage after shock period, the micturition reflex returns. However, the voluntary control is lacking because of absence of inhibition or facilitation of micturition by higher centers. There is hypertrophy of detrusor muscles so that the capacity of bladder reduces. Some patients develop hyperactive micturition reflex.

•UNINHIBITED NEUROGENIC BLADDER

Uninhibited neurogenic bladder is the urinary bladder with frequent and uncontrollable micturition caused by lesion in midbrain. It is also called spastic neurogenic bladder or hyperactive neurogenic bladder.

The lesion in midbrain causes continuous excitation of spinal micturition centers resulting in frequent and uncontrollable micturition. Even a small quantity of urine collected in bladder will elicit the micturition reflex.

•NOCTURNAL MICTURITION

Nocturnal micturition is the involuntary voiding of urine during night. It is otherwise known as enuresis or bedwetting. It occurs due to the absence of voluntary control of micturition. It is a common and normal process in infants and children below 3 years. It is because of incomplete myelination of motor nerve fibers of the bladder. When myelination is complete, voluntary control of micturition develops and bedwetting stops.

If nocturnal micturition occurs after 3 years of age it is considered abnormal. It occurs due to neurological disorders like lumbosacral vertebral defects. It can also occur due to psychological factors. Loss of voluntary control of micturition occurs even during the impairment of motor area of cerebral cortex.