29. *Merkel, C.* Molecular regulation of kidney development: is the answer blowing in the Wnt? / C. Merkel, C. Karner, T. Carroll // Pediatr Nephrol. — 2007. — Vol. 22 (11). — P. 1825–1838.

30. Down regulation of Wnt signaling could promote bone marrow derived mesenchymal stem cells to differentiate into hepatocytes / Z. Ke [et al.] // Biochem Biophys Res Commun. — 2008. — Vol. 367. — P. 342–348.

31. Sera from liver failure patients and a demethylating agent stimulate transdifferentiation of murine bone marrow cells into hepatocytes in coculture with nonparenchymal liver cells / S Yamazaki [et al.] // J Hepatol. — 2003. — Vol. 39. — P. 17–23.

32. *Sawada, R.* Safety evaluation of tissue engineered medical devices using normal human mesenchymal stem cells / R. Sawada, T. Ito, T. Tsuchiya // Yakugaku Zasshi. — 2007. — Vol. 127. — P. 851–856.

33. The bone marrow functionally contributes to liver fibrosis / F. P. Russo [et al.] // Gastroenterology. — 2006. — Vol. 130. — P. 1807–1821.

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ГИСТОФИЗИОЛОГИЯ ОРГАНОВ МОЧЕВЫДЕЛИТЕЛЬНОЙ СИСТЕМЫ

Е. К. Солодова, А. Ф. Максименко

Гомельский государственный медицинский университет

Авторами представлена лекция по теме «Гистофизиология органов мочевыделительной системы» на английском языке. Лекция составлена на основе материала зарубежных учебных пособий, изданных на английском языке для обучения студентов медицинских школ и университетов.

Ключевые слова: почка, нефрон, почечное тельце, проксимальный каналец, дистальный каналец, петля Генле, фильтрационный барьер, собирательная трубочка, моча, юкстагломерулярный аппарат, мочеточник, мочевой пузырь, мочеиспускательный канал.

HISTOPHYSIOLOGY OF THE URINARY SYSTEM ORGANS

E. K. Solodova, A. F. Maximenko

Gomel State Medical University

The authors are presenting the lecture on the topic «Histophysiology of the urinary system organs» in English. The lecture was composed on the basis of foreign textbooks published in English for students of medical colleges and universities.

Key words: kidney, nephron, renal corpuscle, proximal tubule, distal tubule, loop of Henle, filtration barrier, collecting tubule, urine, juxtaglomerular apparatus, ureter, urinary bladder, urethra.

The urinary system consists of the paired kidneys and ureters and unpaired urinary bladder and urethra.

Kidney functions:

1. Production, storage and passing of urine.
2. Excretion.
3. Providing of the electrolyte and water balance.
4. Providing of the acid-base balance.
5. Regulation of blood pressure.
6. Regulation of red blood cells formation.

Development of the kidneys

The source of the kidneys development is intermediate mesoderm — nephrotom. The urinary system develops in a craniocaudal direction and includes three following stages: pronephros, mesonephros and metanephros.

The pronephros differentiates at the end of week 3 in the cervical region and is nonfunctional. It disappears at the end of week 4.

Proliferation of segmented nephrotom cells provides the formation of the pronephric tubules on each side of the body in the cervical region. They fuse with each other forming the two pronephric ducts, which progress towards the cloaca and will be used by mesonephros.

The mesonephros differentiates in week 4 and functions as an interim kidney till the permanent kidney called metanephros is established. The mesonephros regresses in week 8.

The mesonephros is developed from the next nephrotom segments, which form S-shaped mesonephric tubules. The external ends of these tubules open into the mesonephric or Wolffian duct, which is continuation of the pronephric duct.

Internal ends of the mesonephric tubules form the double-layer capsules around the arterial capillary or glomerulus, which are branches of the dorsal aorta. The capsule and glomerulus form the renal corpuscles.

The metanephros differentiates at the beginning of month 2 and begins to function 3 weeks later.

The metanephros is developed from the metanephric blastema, which is nonsegmented homogenous mesodermal mass in the caudal part of embryo body.

The metanephric blastema gives rise to the epithelium of all nephrons parts. The epithelium of the collecting tubules, the papillary ducts, the calyces, the renal pelvis and the ureters differentiate from the metanephric diverticulum, which arises from the lower portion of the Wolffian duct where it opens into cloaca.

General structure of the kidneys

The kidneys are large, bean-shaped organs, surrounded by dense connective tissue capsule.

On the medial border of the kidney there is a depression, the hilum, where nerves enter, blood and lymph vessels enter and exit and the ureter exits.

The parenchyma of the kidney is divided into an outer cortex and inner medulla. In humans the renal medulla consists of 10 to 18 conical subdivisions called renal or medullary pyramids, whose bases are toward the cortex and apices are into the lumen of calyces. The tips of pyramids are called renal papillae or areas cribrosa.

Each medullary pyramid and the associated cortical tissue at base and sides constitute a lobe of the kidney.

The medullary material extends into the cortex as medullary rays of Ferrein. Approximately 400 to 500 medullary rays project into the cortex from the medulla.

Each medullary ray contains straight tubules of the nephrons and collecting ducts. The regions between medullary rays containing the renal corpuscles, the convoluted tubules of the nephrons, and the collecting tubules are called cortical labyrinths.

The cortical material extends into the medulla between the pyramids and forms the renal columns of Bertin.

Loose connective tissue lying in the cortex and medulla between uriniferous tubules is called renal interstitium.

The nephrons of kidney

The main structural and functional unit of the kidney is called the nephron. Each kidney contains about 2 million nephrons. Each nephron consists of renal or Malpighian corpuscle and tubules.

Renal corpuscle includes globular tuft of about 10 to 20 capillaries called glomerulus and surrounding it epithelial Bowman's capsule. Capillaries of the glomerulus are branches of afferent arterioles, one to each glomerulus. The glomerular capillaries reunite to form the efferent arterioles.

The cavity of Bowman's capsule is continuous into nephron's thick proximal segment including proximal convoluted tubule and then proximal straight tubule. The proximal part of the nephron is called thick descending limb.

The thick proximal segment is continuous into a thin segment of the loop of Henle.

The thin segment is continuous into nephron's thick distal segment including first distal straight tubule and then distal convoluted tubule. The distal part of nephron is called thick ascending limb.

The portion of the nephron between a proximal convoluted tubule and a distal convoluted tubule forms the loop of Henle. Thus, the loop of Henle includes 3 parts:

1) proximal straight tubule;
2) thin segment;
3) distal straight tubule.

Types of nephrons

In the kidney there are 3 types of nephrons according to the position of their renal corpuscles in the cortex and the length of the Henle's loop. They are short cortical or subcapsular nephrons, intermediate or midecortical nephrons and long juxtamedullary nephrons.

The juxtamedullary nephrons make up about one eight of the total nephron count.

The cortical nephrons have a short loop of Henle with a very short thin descending limb extending only to the outer region of the medulla. Juxtamedullary nephrons have a long loop of Henle with a very long thin segment with both descending and ascending limbs, extending deep into the inner region of the medulla.

Unlike cortical nephrons the renal corpuscles of juxtamedullary nephrons lie in a deeper region of the cortex on the border with medulla. The renal corpuscles of intermediate nephrons lie in the midregion of the cortex.

The Bowman's capsule

The Bowman's capsule of renal corpuscle has a shape of double-layer cup. The inner layer of the Bowman's capsule toward the glomerulus is a visceral layer, the outer layer is a parietal layer.

The parietal layer of the Bowman's capsule is covered with simple squamous epithelium.

The visceral layer is covered with epithelial cells called podocytes. Podocytes have a cellular body containing a nucleus and several primary processes giving rise to numerous smallest secondary processes also called foot-like processes or pedicels. The elongated spaces between pedicels are filtration slits having about 40 nm width and covered by an ultrathin filtration slit diaphragm.

Filtration slit diaphragm contains a transmembrane protein called nephrin forming a central density with pores and interactions with actin cytoskeleton within the cytoplasm of foot processes. The nephrin regulates the size, patency and selectivity of the filtration slits. Mutations of the nephrin gene are associated with nephrotic syndrome characterized by massive proteinuria and edema.

Filtration barrier of the kidney

There are 2 poles in the renal corpuscle. They are a vascular pole and a urinary pole. In a vascular pole the afferent arteriol enters and efferent arteriol leaves the glomerulus and the afferent arteriol branches into capillaries of the glomerulus.

A urinary pole is the opposite side of the corpuscle, where capsular space is continuous into the lumen of the proximal convoluted tubule.

Structurally the capillaries of the glomerulus belong to the fenestrated type. Endothelial cells of the glomerular capillary and podocytes have common glomerular basal lamina or membrane for both of them.

The glomerular basal lamina is thick (about 0,3 μm) and contains 3 layers. They are a central electron-dense lamina called the lamina densa and internal and external electron lucent layers called the lamina rara interna and the lamina rara externa.

The lamina densa contains collagen type IV which is organized into a network, which acts as physical filter. The lamina rara contains glycosaminoglycans rich in heparin sulfate which affects free passage of proteins with molecular weight less than that of albumin (70,000 daltons or 3,6 nm radius). In diseases of kidneys and diabetes, the glomerular filter becomes much more permeable to proteins.

Albuminuria (presence of albumins in the urine) and hematuria (presence of erythrocytes in the urine) indicate physical or functional damage to the glomerular basal membrane.

Together the glomerular basal lamina, the pedicels of podocytes and the endothelium of the glomerular capillaries form a filtration barrier lying between blood and the cavity of a Bowman's capsule.

Nephrones tubules

In a urinary pole the simple squamous parietal epithelium of the Bowman's capsule is continuous into the simple cuboidal or low columnar epithelium of the proximal convoluted tubule.

Each proximal tubule cell contains a spherical nucleus in an eosinophilic cytoplasm with numerous pinocytotic vesicles and lysosomes. Apical parts of the proximal tubule's epithelial cells have large amount of microvilli with an extracellular glycocalyx, containing enzymes alkaline phosphatase and adenosine triphosphatase. These microvilli form the brush border on the apical parts of the cells.

The basal parts of proximal tubules cells form membrane infoldings with elongated shaped mitochondria lying parallel to the long axis of the cell. This basal part of cells is called basal striation. The basolateral membrane of cells contains active Na+/K+-ATPase («sodium pump»). Diameter of the nephron's proximal tubules is about 60 μm.

The diameter of the Henle's loop thin segment becomes about 15 μm. The epithelium changes to simple squamous in thin segment of the Henle's loop.

Diameter of the nephron's distal tubules is about 35 μm. This tubule is lined with simple cuboidal epithelium. Distal tubule cells do not have the brush border on the apical parts, but their basal parts have well developed basal striation.

The lumen of the distal tubule is generally wider and clear than that of the proximal tubule.

Collecting tubules and ducts

The distal straight tubule is continuous into a collecting tubule, which is connecting or arched collecting tubule joining the collecting duct in medullary ray. The collecting ducts lying in the cortex are cortical collecting ducts and the collecting ducts lying in the medulla are medullary collecting ducts. On the apex of the pyramid the collecting ducts are continuous into collecting or papillary duct of Bellini, opening into calyx.

Together the tubular part of the nephron and the collecting tubule are called «uriniferous tubule».

The collecting tubules and collecting ducts are covered with simple cuboidal epithelium. In the final portion of the papillary duct the epithelial cells acquire a columnar form.

Epithelium of the collecting tubules and ducts consists of 2 types of cells. They are most numerous light pale-stained or CD-cells (collecting duct cells) and less numerous dark or IC-cells (intercalated cells).

Plasma membrane of light principle cells contain hydrophobic transmembrane proteins forming water-channels called aquaporin-2 (AQP-2), which are responsible for water permeability of the collecting tubules and ducts. Mutation of the AQP-2 gene has been linked to congenital nephrogenic diabetes insibitus.

Dark cells are found in the collecting tubules in the cortex and outer medulla but not in the papillary duct. There are α- and β-intercalated cells. The α-intercalated cells secrete hydrogen and reabsorb potassium. The β-intercalated cells secrete bicarbonate and recover chloride.

Urine formation

The first stage of urine formation is called filtration. Filtration takes place in the renal corpuscles of nephrons. It is connected with different diameter of afferent and efferent arteriols (the caliber of efferent arteriol is smaller than the caliber of afferent arteriol). Therefore, higher blood pressure — about 75 mm Hg — arises in the nephrons glomerular capillaries and the blood plasma passes from glomerulus into Bowman's capsule through a filtration barrier. In humans the total glomerular ultrafiltrate or primary urine within 24 hours is from 150 to 200 liters, of which some 99 per cent will be reabsorbed by the uriniferous tubules with 1.5 to 2 liters being excreted as urine.

The efferent arteriol of the cortical nephron is a short vessel, which branches into cortical peritubular capillary network between tubules of the cortical nephron.

In juxtamedullary nephrons the efferent arteriol is continuous into straight vessels called vasa recta. The efferent arteriols of the juxtamedullary nephrons and the vasa recta both branch into a medullary peritubular capillary network. The vasa recta form loops at various levels in the medulla and turn back toward the cortex. The descending and ascending limbs of this loops form a countercurrent exchange system of vessels called a vascular bundle. The descending part of a vascular bundle is an arterial limb or arteriolae rectae and the ascending part is a venous limb or venulae rectae.

Low blood pressure of the peritubular capillary network provides the second stage of the urine formation called reabsorption.

The processes of reabsorption and excretion begin in the proximal convoluted tubules of nephrons. Here all the glucose, amino acids, proteins, about 85 per cent of the sodium are reabsorbed. Chloride ions and water follow passively.

The proteins reabsorption takes place with formation of the pinocytotic vesicles in cells of the

proximal tubules. These vesicles contain proteins macromolecules. The pinocytotic vesicles fuse with lysosomes, where degradation of macromolecules occurs, and monomers are returned to the circulation.

The Na+/K+-ATPase of the proximal tubules basal striation is responsible for transporting sodium ions out of these cells.

The enzymes of the proximal tubules microvilli provide reabsorption of all glomerular filtrate glucose.

The loop of Henle is an essential element in the production of hypertonic urine. The main role of the Henle's loop is to create a hypertonic environment in the renal interstitium of the medulla. This environment plays a very important role in reabsorption of large quantities of water by collecting ducts.

The hypertonicity is achieved by active transport of chloride and sodium ions out of the ascending limb of Henles loop into the medullary interstitium, whereas the ascending limb is impermeable to water. In the descending limb of Henles loop, the wall is freely permeable to sodium and water.

The pumping of sodium continues in the distal convolution of the nephrons.

Hormonal regulation of the urine formation

The aquaporins-2 of the distal convoluted tubules epithelium in terminal portion, collecting tubules and collecting ducts epithelial light cells are regulated by antidiuretic hormone (AND). In the presence of antidiuretic hormone they become permeable to water, which passes out from the tubules to the interstitium of the medulla and the urine becomes hypertonic as water leaves the collecting ducts. If AND is low, the permeability of the distal tubules, collecting tubules and collecting ducts to water is low and little water is removed to the interstitium. Thus, a large volume of diluted urine will be excreted. This condition is called central diabetes insibitus.

Aldosterone acts on the cells of the renal tubules (mostly on the distal ones) to increase the reabsorption of sodium and chloride ions. Aldosterone deficiency in humans with Addisons disease results in an excessive loss of sodium in the urine.

Countercurrent multiplier system

The term countercurrent indicates flow of fluid in adjacent structures of the uriniferous tubule in opposite directions. The ability to excrete hyperosmotic urine depends on countercurrent multiplier system including three structures: loop of Henle, vasa recta and collecting duct.

In loop of Henle, the ultrafiltrate moves within the descending limb of the thin segment toward the renal papilla and moves back toward the corticomedullary junction within the ascending limb of the thin segment. As the thin ascending limb cells add Na+ and Cl– to the interstitium and they are impermeable to water, the interstitium becomes hyperosmotic relative to the luminal content. Some of the interstitium Na+ and Cl– diffuse back at the thin descending limb, but then ions are transported out again in the thin ascending limb and distal straight tubule. This produces the countercurrent multiplier effect. Thus, the concentration of NaCl in the interstitium gradually increases downward the length of the loop of Henle.

The ultrafiltrate that reaches the distal convoluted tubule is hyposmotic. When ADH is present, the distal convoluted tubule, the collecting tubules and the collecting ducts are highly permeable to water. Therefore, in cortex the ultrafiltrate of distal convoluted tubule equilibrates with interstitium and becomes isosmotic. In the medulla, increasing amounts of water leave the ultrafiltrate as the collecting duct passes through the hyperosmotic interstitium and urine becomes hyperosmotic. Therefore the collecting duct of the medulla is postulated as an osmotic equilibrating device.

The vasa recta form a countercurrent exchange system. As the arterial vessels descend through the medulla, the blood loses water to the interstitium and gains salt from the interstitium so that at the tip of the loop the blood is essentially equilibrium with the hyperosmotic interstitial fluid.

As the venous vessels ascend toward the corticomedullary junction, the hyperosmotic blood loses salt to the interstitium and gains water from the interstitium.

The juxtaglomerular apparatus

Juxtaglomerular cells, macula densa and extraglomerular mesangial cells belong to the juxtaglomerular apparatus of the kidney.

Juxtaglomerular cells lay in the walls of afferent and efferent arteriols. A large amount of granules containing enzyme renin is located in its cytoplasm. In the blood the renin influences on the formation of peptide angiotensin I from plasma globulin called angiotensinogen. Then the angiotensin I is transformed into active form angiotensin II by angiotensin-converting enzyme secreted by endothelial cells of the lung capillaries. Angiotensin II is the most potent vasoconstrictor in our organism. As a result, in addition to other functions, the kidneys have a role in the regulation of blood pressure.

Also angiotensin II stimulates zona glomerulosa of the adrenal cortex to release aldosterone.

The macula densa is a part of distal convoluted tubule lying close to renal corpuscles vascular pole between efferent and afferent arteriols. About 20–40 very thin columnar shaped cells of the macula densa form the contact with the juxtaglomerular cells and extraglomerular mesangial cells. Functionally the epithelial columnar cells of the macula densa are sensitive to changes in NaCL concentration in the urine and the decrease in NaCL concentration in the urine leads to stimulation of renin secretion by juxtaglomerular cells.

The extraglomerular mesangial cells are also called Lacis cells. They are located in the angle between efferent and afferent arteriols at the vascular pole. Their function is not clear, but as the endothelial cells of the cortex peritubular capillaries, they may produce hormone erythropoietin stimulating erythropoesis in the bone marrow. The stimulus for erythropoietin release is postulated to be a low concentration of oxygen in the blood of the afferent arterioles.

Mesangium

Mesangial cells lying between glomerular capillaries and their extracellular matrix constitute the mesangium. Functionally the mesangial cells are macrophages because they phagocytose proteins from glomerular basal membrane and plasma proteins, including immune complexes. However, they are not derived from blood monocytes. Mesangial and juxtaglomerular cells are modified smooth muscle cells.

Extracellular matrix produced by the mesangial cells performs the supporting function for podocytes.

The mesangial cells contain contractile filaments and bear receptors to angiotensin II on surfaces. Contraction of mesangial cells could increase intraglomerular blood volume and filtration pressure.

The mesangial cells became prominent in diseases called glomerulonephritis.

Renal interstitium

In the cortex, two types of interstitial cells are recognized: fibroblast and macrophages.

In the medulla, the principal interstitial cells resemble myofibroblast. They are oriented to the long axes of the tubular structures and contain well developed rER, Golgi complex, lysosomes, bundles of actin filaments and lipid droplets. Functionally they may have a role in compressing the tubular structures of the nephrons.

Organs of the urine excretion

Ureters, the urinary bladder and the urethra belong to the organs of the urine excretion. The walls of these organs include 4 layers. They are:

1) mucous membrane — inner layer;

2) submucous membrane;

3) muscularis membrane;

4) adventitia — outer layer.

The mucous membrane of all these organs consists of two sublayers. They are transitional epithelium and lamina propria.

The lamina propria of the mucous membrane, submucous membrane and adventitia are loose connective tissue.

The muscularis membrane is smooth muscle forming inner longitudinal and outer circular layer in the upper and middle part of the ureters. The third outer smooth muscle longitudinal layer also known as oblique is present in the lower part of the ureters and the muscularis membrane of the urinary bladder.

The adventitia covers only the superior surface of the bladder. Its posterior and lateral surfaces are covered with serous.

Urethra

The urethra is a tube which carries urine from the urinary bladder to the exterior. In the male, sperm also passes through it during ejaculation. In the female, the urethra is exclusively a urinary organ.

A longer male urethra includes 3 main parts:

1) Pars prostatic. It is the most proximal part of the male urethra, which passes from the urinary bladder and is surrounded by the prostate gland. In the prostatic urethra, the lining epithelium is transitional. Two ejaculatory ducts and ducts from prostatic glands open into this part of the urethra;

2) Pars membranacea. This is a short part surrounded by striated muscle of the urethra external sphincter. The membranous urethra is lined with pseudostratified columnar epithelium.

3) Pars spongiosa. This is a terminal part of the urethra, which is located in the corpus spongiosum of the penis and is covered with pseudostratified columnar epithelium. The terminal dilatation of the penile urethra called the fossa navicularis, is lined with stratified squamous epithelium. The branched tubular mucous secreting glands of Littre are found along the length of the urethra but mostly in the pendulous part.

A female urethra is shorter and covered with stratified squamous epithelium.

REFERENCES

1. *Beck, F.* Human embryology / F. Beck, D. B. Moffat, D. P. Davies. — USA, Canada, Australia, British: Blackwell Scientific Publications, 1985. — 372 p.

2. *Ben Pansky, Ph.D.* Review of medical embryology / Ben Pansky Ph.D. — New York: Macmillan Publishing Co., Inc., 1982. — 527 p.

3. *Bloom, W.* A textbook of histology: a textbook / W. Bloom, D. W. Fawcett. — Philadelphia, London, Toronto: W. B. Saunders Company, 1975. — 1033 p.

4. *Junqueira, L. C.* Basic Histology: a textbook / L. C. Junqueira, J. Carneiro, J. A. Long. — USA: Large Medical Publications, 1986. — 529 p.

5. *Inderbir, S.* Textbook of human histology with color atlas / S. Inderbir. — New Delhhi: Jaypee Brithers Medical Publishers, 2006. — 364 p.

6. *Lesson, C. R.* Textbook of histology: a textbook / C. R. Lesson, T. S. Lesson, A. A. Paparo. — Philadelphia, East Sussex, Toronto, Mexico, Rio de Janeiro, N.S.W., Tokyo: W.B. Saunders Company, 1985. — 597 p.

7. *Ross, M. H.* Histology: a text and atlas with correlated cells and molecular biology / M. H. Ross, Wojciech Pawlina. — Baltimore, Philadelphia: Lippincott Williams & Wilkins, a Wolters Kluwer business, 2011. — 974 p.

8. *Wheater, P. R.* Functional histology: a text and color atlas / P. R. Wheater, H. G. Burkitt, V. G. Daniels. — Edinburgh, London, New York: Jarrold & Sons Ltd, Norwish, 1980. — 278 p.

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БИОЛОГИЧЕСКИЕ АСПЕКТЫ АПОПТОЗА (обзор литературы)

Н. Е. Фомченко, Е. В. Воропаев

Гомельский государственный медицинский университет

Проблема исследования апоптоза и его взаимосвязь с различными заболеваниями является актуальной в биологии и медицине. Апоптоз — это сложный и многогранный механизм, который возник в процессе эволюции с момента появления многоклеточных организмов, служит в целях регуляции естественного баланса между размножением и гибелью клеток и является необходимым условием поддержания гомеостаза,