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EPIGENETIC MECHANISMS IN THE CONTROL SYSTEM OF THE KIDNEY FUNCTION IN NORM

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Abstract

The publication is devoted to the consideration of the mechanisms of the adaptive capabilities of the kidney in norm, based on epigenetic control systems of protein biosynthesis. This paper emphasizes the high plasticity of epigenetic mechanisms. The thesis that the epigenetic mechanisms have a high degree of plasticity and perform an important function in adaptive reactions of the kidney, is illustrated by data on the epigenetic transformation of key proteins of various nephron sections. In addition, brief information is given on the possible involvement of epigenetic mechanisms in adaptive rearrangements of arginine vasopressin and natriuretic peptides. High plasticity, accuracy and power of epigenetic systems regulating the adaptive capabilities of the kidney are emphasized.

Key words: kidney; adaptation; epigenetics.

INTRODUCTION

Epigenetic systems of management expression genes perform fundamentally important function on different stages ontogeny. For example, the fetus they coordinate normal flow nephrogenesis. In adulthood, epigenetic mechanisms are closely involved in the control system of the homeostatic functions of an organ. The processes declines functions kidney at the elderly people also closely connected with epigenetic mechanisms.

Evaluating role epigenetic mechanisms at processes organogenesis kidneys, must be mark role methylation histones at cytodifferentiation embryonic cells (Adli M et al., 2015). Alongside with This highlights role of balance activity histone acetyltransferase and deacetylase at regulation expression genes on early stages organogenesis buds (Hilliard SA, El-Dahr SS, 2016). Speaks out opinion about that some deacetylase histone proteins (HDAC1 and HDAC2) can be critically are important for processes development tubular and vascular components nephron on early stages ontogeny kidneys (Liu H et al., 2018). Alongside with this, in literature there are data about that the synthesis of non-coding RNA and reactions acetylation histones perform important role at formation juxta-glomerular apparatus (JGA) in process nephrogenesis (Martini AG, Danser AHJ, 2017). With other hand, intraorgan products components renin-angiotensin systems (RAS) on early stages ontogeny is also critically important for coordination histo- and organogenesis. It established that excess consumption chloride sodium in time of pregnancy can violate these processes through changes activity intraorgan expression of components of the PAC and products oxide nitrogen at tissues fetus (Stocher DP et al., 2018). Analysis roles methyltransferase and demethylase, and also histone-acetyltransferase and Histone-deacetylase at processes nephrogenesis allowed to reveal certain patterns of activity dynamics data groups enzymes as they form nephron (Hilliard SA, El-Dah SS, 2016). The authors quoted review match processes nephrogenesis with topology and time dynamics of activity systems covalent modifications Chromatin: residues lysine at composed histones (H3K), residues arginine at composed histones (H3R) and molecules DNA. Alongside with by processes covalent modifications chromatin mechanisms transcriptions and metabolism noncoding RNA also can have fundamentally important value for of normal currents morphogenesis kidneys mammals (Ho J, Kreidberg JA, 2012). At the present time role microRNA at processes organogenesis kidneys studied enough in detail. At literature there are intelligence about that some families microRNA critically are important for morphogenesis vascular-glomerular and tubular departments kidneys (Trionfini P, Benigni A, 2017). Perhaps epigenetic mechanisms organogenesis kidneys are located under control hormones system actions maternal organism. At specifically, is shown it that such by ability can have melatonin (Tain Y.-L. et al., 2017). By opinion authors, melatonin possesses by ability to control not only formation architecture nephron, but and to regulate level activity intrarenal systems NOsynthase and renin-angiotensin systems fetus through intensity methylation DNA and acetylation proteins histones. Besides that shows that insulin also possesses pronounced influenced on state epigenetic mechanisms at tissues kidneys human (Lay AC, Coward RJM, 2018).

At literature are given data about that hypomethylation chromatin on level neuro-endocrine the link of control activities kidneys - one of reasons withering homeostatic functions body at elder age (Murgatroyd C et al., 2010). Further research allowed to establish

important value roles methylation chromatin at age changes systems of control water-salt of balance at mammals (Greenwood MP et al., 2018). AT literature given to Attention the roles of microRNA and covalent modifications chromatin at processes age violations functions kidney human (Shiels PG et al., 2017). On basis analysis roles deacetylase histone sirt1 and sirt3 in regulation exchange processes kidney being done conclusion about that given Group enzymes possesses pronounced nephroprotective property, providing containment processes aging tissue organ (Morigi M et al., 2018).

PLASTICITY OF SYSTEMS OF EPIGENETIC MODULATION OF EXPRESSION OF RENAL PARENCHYMA GENES

As already noted above mature age epigenetic mechanisms retain important a place at regulation of renal function, in particular, adaptive reactions renal parenchyma. Required emphasize that epigenetic mechanisms of control biosynthesis squirrel preserve tall level plasticity at mature age. Illustrating high indicators plasticity discussed processes, you can mention role methylation DNA at formation daily allowance rhythm behavioral activity mammals (Azzi A et al., 2014). Consequently, est the grounds to believe that molecular mechanisms regulation expression genes can directly coordinate adaptive responses of the renal parenchyma. Perhaps epigenetic mechanisms, as well as with neuro-humoral systems of control water-salt exchange, accept participation at regulation of homeostatic functions of the kidneys.

At row publications states that stimulus for molecular mechanisms of management expression genes as usually a dynamics parameters constants water-salt of balance organism. results more early research showed that methyltransferase histone Dot1a directly determines aldosterone-dependent transcription gene EnaC-alpha at distal departments nephron (Zhang D et al., 2009). According to according to literature, state posttranscriptional processing predecessor miRNA at proximal nephrocytes can perform key role at adaptations tubular epithelium to ischemia, possibly participating at pathogenesis reperfusion lesions S3-segment (Wei Q et al., 2010). Stresses that intensity reparative reactions renal parenchyma can be monitored noncoding RNA and condition methylation H2A and H3 histones (Chou Y-H et al., 2017). At literature there are intelligence about that at of some species mammals at adaptive reactions kidneys on sharp changes systemic parameters water-salt exchange can take participation mechanisms regulation expression genes (MacManes MD, 2017). Alongside with this, in proximal segment nephron an object regulatory influences epigenetic mechanisms are genes subunits sodium/potassium ATPase basolateral membranes epithelium (Taub M, 2018). By opinion the author quoted review, signal for activation/inactivation transcriptions specified genes can serve concentration sodium at luminal liquid, and the direct implementation of the incoming signals is determined by the intensity acetylation histones. Alongside with by this, changes intracellular concentration sodium at epithelium proximal segment nephron and fine ascending loops Henle also can render direct influence on state transcriptions genes transport proteins expressed by this by population nephrocytes (Gildea JJ et al., 2018). Are given data about that content sodium at diet power supply renders influence on expression genes proteins-transporters sodium (ENaC and Na-Cl -cotransporter) in distal department nephron (Ivy JR et al., 2018). With other hand, is shown it that hyponatric diet stimulates hypomethylation gene aldosterone-synthase through activation RAS (Takeda Y et al., 2018). Attracts attention that fact that nuclear deacetylase renal parenchyma (SIRT1,3,6,7) possess by ability to regulate expression row proteins at tissues kidneys with fundamental value for homeostatic functions organ (Morigi M. et al., 2018). At Specifically, the authors

review report that SIRT1 directly regulates expression alpha-subunit epithelial sodium canal, endothelial NOsynthase and receptor to angiotensin-2 (AT1R) in podocytes and smooth muscle the fibers of the blood vessels of the kidney. By according to authors SIRT3 involved at regulation exchange processes at mitochondria, has anti-inflammatory and antisclerotic action. protein SIRT6 also is required for deterrence sclerosing factors.

Should note that, in addition with covalent modification chromatin important role at epigenetic control of renal transport substances relegated non-coding RNA (Hua JX et al., 2012). Shown important role microRNA at regulation of transport sodium at epithelium nephron (Mladinov D et al., 2013). Alongside with ion control by function kidney, found that noncoding RNA can take participation at management osmoregulating by function mammalian kidneys (Huang W et al., 2011; Luo Y et al., 2014). The authors quoted publications indicate on role microRNA at regulation expression transport proteins medullary segments nephron at answer on acute hyperosmotic stimulus. Should noted that at the norm expression of some types microRNA at cortical and cerebral layer kidneys It has clear differences (Chandrasekaran K et al., 2012; Ichii O, Horino T, 2018). Is given information about direct influences hyperosmotic stimulus on expression strictly certain types microRNA in internal kidney medulla (Chandrasekaran K et al., 2012). Together with the authors are turning attention the fact that the state of the microRNA metabolism in renal parenchyma can be regulated by humoral factors of neuro-endocrine the link control homeostatic functions the kidneys. With this microRNA controls the transport of ions not only in the kidney, but also the system parameters of ion homeostasis (Hua JX et al., 2012). At row publications underlined thesis about that microRNA can realize constant thin regulation exchange processes at renal parenchyma. For example, there are messages about roles microRNA at regulation exchange processes at podocytes, in dependencies from possible changes magnitudes hydrostatic pressure at ball and chemical composition ultrafiltrate (Trionfini P, Benigni A, 2017).

One of most promising directions research roles micro RNA at regulation activities kidneys is an analysis relationship intra organism metabolism of micro RNA and their content in the biological media of the body (Thomas MJ et al., 2018). With points of view practical medicine, value such research due to by necessity introductions new methods diagnostics and therapies diseases kidneys (Trionfini P, Benigni A, 2017; Thomas MJ et al., 2018).

Together with in a significant attention given to roles humoral systems of control homeostatic functions kidney at regulation expression genes at renal parenchyma (Hirohama D et al., 2018; Lu CC et al., 2018). The data are given about molecular mechanisms regulation of local expression of protein-components RAS (Martini AG et al., 2017; Lu CC et al., 2018). Earlier was is shown role microRNA at regulation expression genes renin (Sequeira-Lopez MLS et al., 2010). At the present time installed role methylation DNA acetylation and methylation histones tubular epithelium at management expression gene angiotensinogen (Marumo T et al., 2015). Shown participation methylation DNA covalent modifications histones and metabolism micro RNA at expression genes renin at kidney (Martini AG, Danser AHJ, 2017). With other hand, revealed value renin-angiotensin-aldosterone systems at regulation expression genes transport proteins tubular department nephron at answer on change physiological constants water-salt balance (Hirohama D et al., 2018). It established that covalent modification histones (methylation and acetylation) may take participation at control expression gene atrial natriuretic peptide (Hohl M et al., 2013). Reported that epigenetic control expression gene atrial natriuretic peptide promotes adaptive changes products hormone (Sergeeva IA et al., 2016). With this, atrial natriuretic peptide also being considered at quality inductor epigenetic mechanisms implemented through specific

microRNA (Li Y et al., 2016). Not less interest attract intelligence about influences acute osmotic stimulus on epigenetic systems of control synthesis arginine-vasopressin - AVP (Hayashi M et al, 2006; Greenwood MP et al., 2016). It should be noted that sex steroid hormones can also affect the expression of the AVP gene with the participation of epigenetic mechanisms (Augera CJ et al., 2011). Since the tubular effects of AVP are realized with the participation of specific porobasing proteins - aquaporins, in particular, with the participation of aquaporin-2 (AQP2), information about the significance of the epigenetic control of this protein attracts interest (Park E-J, Kwon TH, 2015; Jung HJ, Kwon T-H, 2016).

ENDOCRINE FACTORS OF REGULATION OF WATER-SALT BALANCE OF THE ORGANISM IN THE SYSTEM OF EPIGENETIC MECHANISMS OF REGULATION OF HOMEOSTASIS

Assuming a role of epigenetic mechanisms in the regulation of homeostatic functions of the kidney and adaptive body changes, in our opinion, it is necessary to analyze, firstly, information on the role of epigenetic mechanisms in modulating the expression of genes of protein hormones-regulators of water-salt metabolism. Secondly, the properties of humoral factors of systemic action, as possible inducers of the epigenetic transformation of the renal parenchyma. The role of arginine-vasopressin as a systemic regulator of osmotic homeostasis, which determines the acute and precise response of an organism to changes in the nutritional and intravenous fluids of osmotically active substances (Bourque CW, 2008; Thornton SN, 2010; Greenwood MP et al., 2015; Park E-J, Kwon T-H, 2015). The physiological role of the renin-angiotensin system is defined as the control of the reabsorption of a very significant amount of ultrafiltrate, sodium and potassium dissolved in it, as well as other vital components of the ultrafiltrate (Zhuo JL, Li XC, 2001; Kurtz A, 2012; Gomez RA, Sequeira-Lopez MLS, 2018). Thus, Angiotensin-II participates in the regulation of ionic, osmotic, volemic, acid-base homeostasis, and also regulates the tone of blood vessels. Atrial (brain) sodium uretic peptide is the most important humoral regulator of volemic homeostasis, which determines the excretion of sodium and fluid at the level of the distal nephron (Kuwahara K, Nakao K, 2010; Nakagawa Y et al., 2019).

a). ARGININE VASOPRESSIN (AVP)

The results of earlier studies have shown that changes in the physiological constants of osmotic and volemic homeostasis affect the transcription levels of the arginine vasopressin gene (AVP) (Kondo N et al., 2004). In addition, the authors of the cited publication revealed a correlation between the concentration of sodium cations in the extracellular fluid and the expression level of the arginine vasopressin gene. A dramatic increase in the transcription of the AVP gene under the influence of an osmotic stimulus was also demonstrated (Hindmarch CCT, Murphy D, 2010). Along with this, it was shown that the hyperosmotic stimulus enhances the transcription of a number of genes whose proteins accumulate in the posterior lobe of the pituitary (Hindmarch C et al., 2006). It was found that activation of transcription of the arginine vasopressin gene, under the influence of osmotic exposure, demonstrates a more pronounced sensitivity to the stimulus, compared with other neuropeptides of the posterior pituitary gland (Yue C et al., 2008). The difficulty is that the genes of the hypothalamic-pituitary axis, which are involved in the regulation of the reproductive sphere, are also sensitive to the osmotic stimulus (Qiu J et al., 2007). At the same time, it was found that osmotic loads have a specific effect on the expression of a well-defined group of genes in

the supraoptic rat nucleus (Johnson KR et al., 2015). At the same time, it should be noted that, probably, the arginine vasopressin gene contains a nucleotide sequence in the promoter region, which is sensitive to changes in osmotic homeostasis indicators (Ponzio TA et al., 2012). The authors established a difference in the primary nucleotide sequence of this part of the arginine vasopressin and oxytocin genes. Further, comparing the classical scheme of physiological control of osmotic homeostasis and the facts confirming the involvement of epigenetic mechanisms, based on the above research results, we state that the expression index of the arginine vasopressin gene is sensitive to osmolality shifts of extracellular body fluid. The likely mechanism of the influence of the physicochemical conditions of extracellular fluid (sodium chloride concentration in extracellular fluid) on the state of transcription of the arginine vasopressin gene was mainly confirmed by previous observations (Kondo N et al., 2004; Hindmarch CC, Murphy D, 2010) . It is noted that AVP, in addition to the regulation of osmotic homeostasis, may be responsible for behavioral reactions, therefore, from the point of view of the authors, violations of osmotic homeostasis may adversely affect adaptive behavioral reactions (Mitchell NC et al., 2018). Arginine vasopressin gene expression has been shown to exhibit a high level of plasticity, and that the intensity of DNA methylation in the region promoter of the hormone gene can vary significantly depending on the state of the osmotic homeostasis indicators of the body (Greenwood MP et al., 2016). It is reported on the species-specific molecular mechanisms involved in the induction of arginine vasopressin transcription, on the background of dehydration of the organism (Stewart L et al., 2011). The high plasticity of epigenetic control systems for arginine biosynthesis of vasopressin is confirmed by the fact that the increased transcription of the hormone gene is detected under conditions of acute hyperosmotic stimulus with sodium chloride solution (Kawasaki M et al., 2009). Currently, there are data on which enzymatic systems responsible for the covalent transformation of chromatin are involved in changing the transcription of the arginine vasopressin gene (Archer T, 2015). Further studies conducted by researchers from the Murphy D group showed that a number of genes (Caprin2) are sensitive to osmotic stimuli, proteins of which may be important in shaping the adaptive response of the hypothalamic supraoptic nuclei to changes in osmotic homeostasis of the body (Loh S-Y et al., 2017). Given that the role of the Caprin2 gene in the mechanisms of stabilization of the matrix RNA arginine vasopressin has been shown (Konopacka A. et al., 2015). This thesis can be supplemented with the information that microRNA are also involved in the epigenetic modulation of the activity of neuro-endocrine control of osmotic homeostasis (Luo Y et al., 2014).

In this block of analysis of literature data, it is necessary to highlight the fact that arginine vasopressin can directly control the expression of the transport protein Na +, K +, 2Cl-cotransporter in the ascending loop of Henle nephron (Konopacka A et al., 2015). However, directly enhancing the expression of the Na +, K +, 2Cl-cotransporter gene by the effect of arginine vasopressin is considered as a long-term AVP-dependent protein stimulation (Knepper MA et al., 2015). At the same time, the authors of the review emphasize that arginine vasopressin can control the expression of such transport proteins in the distal segments of the nephron, such as sodium chloro transporting protein, urea carrier, some subunits of the sodium channel epithelial pore-forming proteins of aquaporins. The relevance of these mechanisms in the study of the pathogenesis of diseases of the kidneys and the cardiovascular system (Qian Q, 2018) is emphasized. AVP-dependent systems of intracellular signal transduction (through protein kinase) are also analyzed in the epithelium of the collecting tubules of the tubular nephron, as a link inducing epigenetic control of the expression of transport protein genes (Sanghi A et al., 2014). On the other hand, the

interrelation of various isoforms of adenylate cyclases and protein kinases in the system of regulation of transport protein genes in the epithelium of collecting tubules is analyzed (Roos KP et al., 2013).

Concluding consideration of the role of epigenetic mechanisms in maintaining osmotic homeostasis, it should be noted that AVP is involved in long-term stimulation of aquaporin-2 biosynthesis and expression in the epithelium of the collecting tubule of the nephron tubule (Wilson JLL et al., 2013). The mechanisms of activation of transcription of the aquaporin-2 gene, including the mechanisms of intracellular signal transduction, were identified, and DNA regions of the putative transcription regulator binding were identified (Yua M-J et al., 2009). The analysis of the metabolism of aquaporin-2 protein in the epithelium of the collecting tubule of the tubule nephron and the role of AVP in the management of the transcription of the AQP2 gene (Jung HJ, Kwon TH, 2016). Along with this, the authors of the cited review indicate the role of microRNA (miR-32 and miR-137) in the processes of intracellular metabolism of aquaporin-2 protein. Assessing the role of epigenetic control of the physiological functions of collecting tubules (Xiao Z et al., 2016), the authors conclude that the balance of nuclear methyltransferase (Dot1lAC and Dot1lf / f) activity in the epithelium of this nephron segment can have a significant effect on the expression of aquaporin protein -2 Since changes in the production and biological effects of arginine vasopressin are related not only to the regulation of water-salt homeostasis, but also to human behavioral responses, the study of epigenetic control processes, for example, WUA receptors, is also a subject of interdisciplinary research (Bodden C et al., 2017).

b). SODIURETHIC PEPTIDES

The interest in epigenetic control systems of ANP is also to some extent due to the neurotropic effects of the hormone (Frieling H. et al., 2008). The physiologically active substances capable of inducing transcription of atrial (ANP), brain (BNP) and C-type natriuretic peptides, structure of genes and natriuretic hormones themselves (Gardner DG et al., 2007; Kuwahara K, Nakao K, 2010; Ichiki T, Burnett JC, 2017; Nakagawa Y et al., 2019). However, there is evidence that ANP can be synthesized by the epithelium of the tubule nephron (Dong L et al., 2016; Pandey KN, 2018). At the same time, in some review publications there is a thesis about the important practical significance of research on the epigenetic control of the expression of natriuretic peptide genes (DiSalvo TG, 2015; Man J et al., 2018). Since several aspects of this problem are of interest: the efficiency of using the parameters of the synthesis and secretion of natriuretic peptides as diagnostic markers of a number of topical nosologies, research into the actual mechanisms controlling the expression of these hormones' genes and the involvement of certain hormones and cytokines involved in the pathogenesis of cardiovascular diseases and kidney: angiotensin-2, transforming growth factor-beta1, thyroid hormones (Sergeeva IA, Christoffels VM, 2013). At the same time, literature data emphasize the importance of the expression of receptors of natriuretic peptides in the cardiovascular system and renal parenchyma for understanding the physiological and pathophysiological effects of hormones (Pandey KN, 2011; Kumar P et al., 2014).

Experimental studies have shown that hypertrophy of toxic genesis of cardiomyocytes is accompanied by a decrease in miR-133a production against the background of increased DNA methylation by DNA transforms of DNMT1 and DNMT3b, as well as a dose-dependent increase in m-RNA level of ANP and BNP (Huang L et al., 2016). A decrease in the level of miR-133a in the myocardium was detected in laboratory rats subjected to prolonged infusion of angiotensin-2 (Li Y et al., 2016). At the same time, the authors report that prior

administration of recombinant ANP to animals had a positive effect on the dynamics of miR-133a. Under non-ischemic cardiomyopathy, a decrease in the expression of the ANP and BNP genes in cardiomyocytes was observed against the background of increased methylation of the lysine H3 residue of the histone nucleosome (Ito E et al., 2017). Along with this, the authors of the publication revealed a relationship between the biosynthesis of ANP in cardiomyocytes and the production of (miR-133a) microRNA. The results of further observations showed that microRNA-30 may participate in the regulation of the synthesis of BNP (Nakagawa Y et al., 2019). An important role in the regulatory effect of the hormone is assigned to its receptors. In this sense, attention is drawn to the fact that the expression level of the A receptor for the natriuretic peptide, the most physiologically active receptors for ANP (BNP), negatively correlates with the enzymatic activity parameters of the DNA methyltransferase isoform DNMT3B (Shen K et al., 2017). Along with this, an opinion is expressed on the key role of histone protein deacetylases (HDAC4) in regulating the expression of ANP and BNP genes in normal conditions and in pathology (Hohl M et al., 2013). As a result of experimental studies, it was found that impaired functional state of the myocardium is accompanied by changes in the production of ANP and BNP against the background of demethylation of H3K9 in the promoter regions of the genes of these proteins and a moderate increase in histone acetylation of H3 (H3K27ac) (Sergeeva IA et al., 2016). Then the indices of acetylation of H3K9 were not significantly changed. Previously obtained information also emphasizes the role of histone protein acetylation in the regulation of receptor expression of the A population to the natriuretic peptide in the renal parenchyma, (Kumar P, Pandey KN, 2009). According to the authors of the cited publication, acetyltransferase of histone proteins (P300), with the participation of specialized microRNA, can regulate the expression of the guanylyl cyclase-A / receptor-A gene of the natriuretic peptide. In further studies, the authors showed that the epigenetic mechanism for regulating the expression of guanylyl cyclase-A / receptor-A of the natriuretic peptide (Npr1) based on the histone acetylation balance (acetyltransferase P300 and histone HDAC1 deacetylase) can play an important role in maintaining the physiological constants of volistic organism homeostasis (Kumar P et al., 2014). However, the authors suggested that the magnitude of the osmotic pressure in the extracellular fluid, the level of production of angiotensin-II and vitamin D may affect the indicators of Npr1 gene expression.

It is emphasized that gene amplification (Nppa and Nppb), as well as natriuretic peptide receptors, prevents an increase in blood pressure, enhances renal blood flow, increases the glomerular filtration rate, limits the processes of inflammation and fibrosis in the renal parenchyma (Pandey KN, 2018). The authors of the cited review also indicate that natriuretic peptides have the ability to inhibit the activity of the renin-angiotensin-aldosterone system. Attention is drawn to the fact that a significant number of publications on this topic mark the antagonism of the physiological effects of natriuretic peptides and the transforming growth factor beta1 (TGF beta1). The reason for such attention, in our opinion, is explained by the fundamental role of TGF beta1 in a number of pathogenetic mechanisms of dysfunction of the organs of the cardiovascular system and the kidneys (Chen L et al., 2018). In this sense, it is appropriate to provide evidence that TGF beta1 can influence the system of natriuretic peptides by suppressing the transcription of the Npr1 gene, the main hormone receptor in the muscle layer of the aorta wall of laboratory mice (Sen A et al., 2016).

Conclusion

A brief review of the literature data showed that epigenetic systems for controlling gene expression perform a very important function in adaptive kidney responses in normal

conditions. In our opinion, a significant contribution of epigenetic mechanisms is determined by their high degree of plasticity, power and accuracy. The property of plasticity is the determining quality in adaptive reactions of the kidney. Their power is realized due to the cumulative effect of the combined epigenetic transformation of the renal parenchyma and the neurohumoral control systems of the water-salt balance. Accuracy implies an adequate, maximally effective response of the efferent organ to systemic changes in homeostasis.

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