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Effect of lithium carbonate on kidney structure in conditions of distant tumor growth

The effect of lithium carbonate on kidney structure when used as an antitumor agent was studied in an experiment on CBA mice. Tumor growth was simulated by introducing hepatocarcinoma-29 cells into the muscle tissue of the right thigh of experimental animals. Lithium carbonate was administered to animals per os. Kidney structure was studied by light, electron microscopy and morphometry after 30 days of experiment. The dynamics of distant tumor growth in the kidneys revealed structural changes, indicating a violation of organ function. It is shown that the 30 th day of tumor development there is a decrease in size of lumen of the capsule of the renal corpuscle, the increase in volumetric density of capillary glomeruli, enlarged interstitial spaces of the renal corpuscle. Noted swelling of the cytoplasm of the podocytes, the increase in the number sitapati, reducing the fenestre in endothelial cells of glomerular capillaries, swelling of epithelial cells of proximal and distal kidney, as well as reducing the thickness of the basal membranes (BM) of the distal and proximal tubules. The use of lithium carbonate as an antitumor agentled to the aggravation of structural changes in the kidneys, which, apparently, was due toan increase in the toxic load on the organ due to the increase in the decay products and death of tumor cells under the influence of lithium.

Keywords: lithium carbonate, hepatocarcinoma-29, kidney, kidney filtration barrier, ultrastructure.

Introduction

In spite of the considerable scientificinterest in the state of kidneys at various pathological conditions of an organism, these changes have not been sufficiently studied yet [1].

The hepatocarcinomais related toone of the aggressive human tumors and gives a high percentage of mortality among patients due to metastasis [2]. It is known that lithium compounds (lithium chloride and lithium carbohydrate) can affect the signaling and regulation of the cell cycle [3], they have an immunomodulatory properties [4]. It was revealed that lithium act through the suppression of the activity of glycogen synthetase kinase-3β may have an effect on the development of apoptosis, the activity of the factor of the growth of vessels, neutrophil chemotaxis, etc. [5]. In some works have been shown the effectiveness of the use of lithium compounds for suppressing tumor growth [6–8]. The same lithium compounds consider as potential agents of the target therapy, which are able to slow down the growth of the tumor [9].

Until now, there is no evidence of the effect of lithium on structure of kidneys, when used as an antitumor drug. Kidneys are exceptionally important for the life of an organism. They perform many functions, the main of which are:

– purification of an organism from toxic substances (as being produced in the process of vital activity of an organism, soand emanating from outside);
– removingof excess fluid;
– the production of the hormone erythropoietin, necessary for the maintenance of the normal level of the hemoglobin (Hb);
– the elimination of calcium, phosphorus and vitamin D_3;
– maintaining blood pressure;
– maintenaningof acid-base condition;
– maintaining the nutritional condition of the body [10].

The kidneys are the organ of converting proteins, lipids and carbohydrates. Under fasting conditions, up to half of glucose from organicacids is formed in the kidneys, which enters tothe blood [11]. Kidneys play an important homeostatic role in the body [12]. The kidney is fraught with different types of endothelium, each

with specific structural and functional characteristics. The glomerular endothelium, which is highly fenestrated and coated with a rich glycocalyx, participates in the sifting properties of the glomerular filtration barrier and in maintaining the structure of the podocytes. Microvascular endothelium in peritubular capillaries, which is also fenestrated, transports reabsorbed components and participates in the function of epithelial cells [13]. Microanatomy of the kidney, as well as the ultrastructural organization of the nephron is normally well described [14]. A highly organized vascular system is necessary for kidney function, and impaired circulation in the nephrons leads toorgan failure. Each nephron contains a bundle of capillaries inside the glomerulus, which performs ultrafiltration of blood [15]. The unique permeability characteristics of the glomerular capillary wall depend on its three-layer structure consisting of endothelial cells, basal membrane and podocytes. These components form a glomerular filter barrier [16].

The study of the influence of malignant growth and anticancer drugs on the structural and functional state of the kidneys is relevant.

Objective: to identify the biological effect of lithium carbonate on the structural organization of the kidney when it is used tocorrect tumor growth.

Material and methodology

The experimental study was conducted on male mice of the CBA line weighing 18–20 g at the age of 3 months in the SPF vivarium of Institute of Cytology and Genetics of the Russian Academy of Sciences (Novosibirsk city). The animals were kept on a standard diet with free access to water and food. Work with animals was carried out in accordance with the«Rules of work with the use of experimental animals».4 groups of animals were used in the experiment. Group 1 included intact mice (n = 5); group 2 included animals with tumor development (n = 10). Hepatocarcinoma-29 (Hc-29) cells were used to induce tumor growth (n = 20). Hepatocarcinoma-29 was obtained and verified by the Institute of Cytology and genetics of the Russian Academy of Sciences. Hc-29 cells were transplanted into the abdominal cavity of the CBA line mice, after 10 days, ascitic fluid was taken, suspended in a 10-fold volume of saline solution and 0.1 ml of intact animals were injected into the muscle of the right thigh. The 3 group of animals (n = 10) included intact mice that were administered per os of lithium carbonate. Group 4 animals (n = 10) after the induction of the tumor process broke per os lithium carbonate. Lithium carbonate was administered in saline at a rate of 125 mg/kg weight. The choice of lithium carbonate dose of 125 mg/kg wt for per os administration was based on known experimental datain which serum lithium levels in treated animals were in the range of 0.7–1.2 mmol/L. Lithium carbonate in saline solution was injected with a probe every other day during the 30 days. Sampling of material for research was carried out after 30 days of the experiment. Animals were removed from the experiment under ether anesthesia by cranio-cervical dislocation.

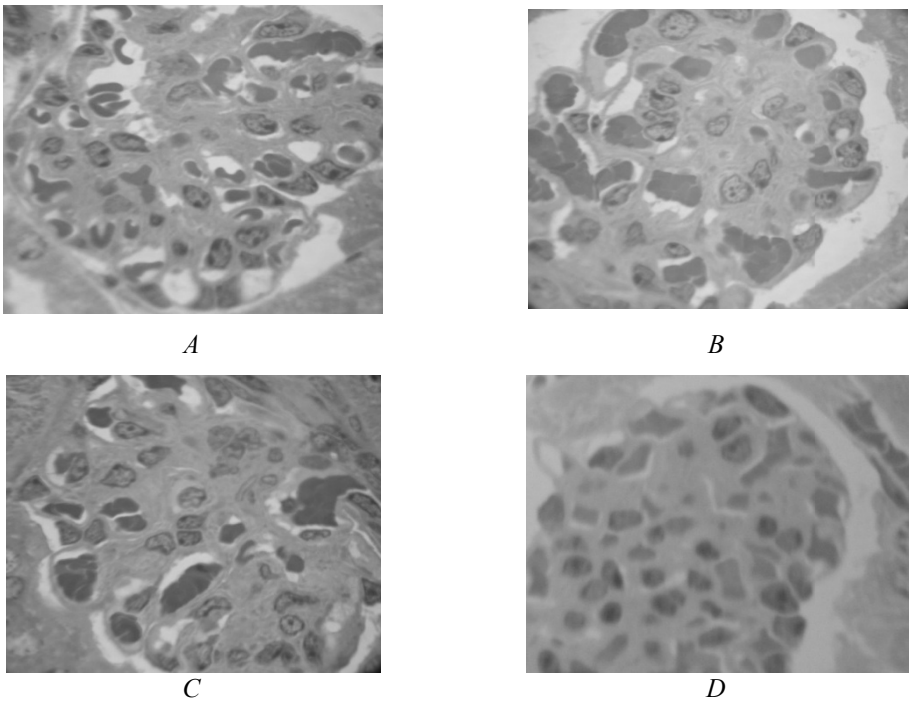
For electron microscopic examination, kidney samples were fixed in 4 % paraformaldehyde solution prepared on Hanks medium, fixed for 1 hour in 1 % OsO_4 (osmium tetroxide) solution (Sigma, USA) on phosphate buffer (pH=7.4), dehydrated in ethyl alcohol of increasing concentration and enclosed in EPON (Serva, Germany). Half-thin slices with a thickness of 1 micron were obtained on the ultramicrotome Leica EM UC7 (Germany/Switzerland), stained with toluidine blue, studied under a light microscope «LEICADME» (Germany), photographed using acomputer program «Avigion».

Ultrathin sections 70–100 nm thick were contrasted with saturated aqueous solution of uranyl acetate and lead citrate and studied in electron microscope JEM 1010 (Japan). At ×12000 magnification, electronograms of fragments of renal cells, epithelial cells of the proximal and distal parts were obtained. The obtained micrographs were morphometrized using acomputer program Image J.

We determined the volume densities of capsule lumen, capillary glomeruli, interstitial spaces of renal corpuscle, diameters of proximal and distal nephron epithelial cells, sizes of basal membranes of glomerular capillaries and epithelial cellsof proximal and distal nephron. Statistical processing of the obtained results was performed using the software package STATISTICA V. 6 (StatSoft Inc., U.S.) The mean values and standard deviation were calculated, the reliability of the differences was calculated by the Mann-Whitney U-criterion, at aconfidence level of 95 % ($p < 0.05$).

Results and discussions

After 30 days of the experiment, in animals with tumor growth without treatment, in the structure of the kidney, an increase in the size of the lumen of the renal cell capsule was noted by 18 % (Fig. 1).



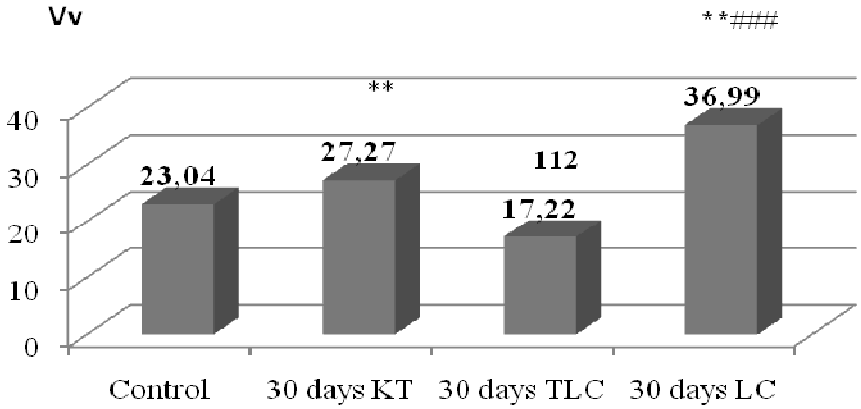
A *B*

C *D*

A — control; *B* — after 30 days of tumor development. Increase of glomerular capsule lumen; *C* — maintenance of lithium carbonate per os by intact animals; *D* — maintenance of lithium carbonate per os by animals with tumor growth. Coloration by toluidine blue. Increase ×400.

Figure 1. Structure of the renal corpuscle of CBA mice

We noted that the addition of lithium carbonate per os, a 25 % decrease in the size of the lumen of the renal cell capsule (Fig. 2).



Vv — volume density, %: **P < 0.001; ***P < 0.0001 with respect to the control group; $^{###}$P < 0.0001 in relation to the group with tumor growth without treatment; ^{11}P < 0.001, ^{111}P < 0.0001 in relation to the group with tumor growth without treatment; ^{2}P < 0.01, ^{22}P < 0.001 in relation to group c administration of per os lithium carbonate to intact animals. 30 days OP — the development of tumor growth hepatocarcinoma-29; 30 days OKL — tumor growth with the introduction of per os lithium carbonate; 30 days CL — the introduction of per os lithium carbonate intact animals

Figure 2. Volume density of the capsule of the renal body y of animals in the dynamics of tumor growth of experimental hepatocarcin-29 in the muscle tissue of the thigh and with the introduction of lithium carbonate per os

When per os lithium carbonate administered into intact animals, in the structure of the kidney there was an increase in the size of the lumen of the renal cell capsule by 60 %.

The volume density of capillary glomeruliin animals with tumor growth without treatment decreased by 25 %. When administered per os lithium carbonate toanimals with tumor growth, the value of this parameter increased by 9 %, and when administered lithium carbonate tointact animals decreased by 19 %.

The size of interstitial spaces of the renal body of animals with tumor growth without treatment was increased by 25 %, with the introduction of lithium carbonate per os increased by 4 %, with the introduction of lithium carbonate per os intact animals decreased by 26 % (Table 1).

Table 1

Volume density of structures of renal corpuscles of mice of the line CBA

Characteristics, Vv, %	Groups (M±SD)			
	Control	30 quotes of the tumor growth	30 quotes of the tumor growth + lithium per os	Injection of lithium per os intact animal
Capsule lumen	23.04±9.04	$27.27±7.12^{**}$	$17.22±5.56^{112}$	$36.99±11.19^{**\#\#\#}$
Glomerular capillaries	36.78±7.49	27.65±7.08	$39.93±5.68^{22}$	$29.88±7.95^{***\#\#\#}$
Intercellular space	23.44±7.42	$29.30±6.76^{**}$	$24.31±6.18^{22}$	$17.40±7.54^{***\#\#\#}$

Note: Vv — volumetric density, %:
$^{**}P<0.001$; $^{***}P<0.0001$ in relation to the control group;
$^{\#}P<0.0001$; $^{\#\#\#}P<0.0001$ in relation to the group with tumor growth without treatment;
$^{11}P<0.001$; $^{111}P<0.0001$ in relation to the group with tumor growth without treatment;
$^{2}P<0.01$; $^{22}P<0.001$ in relation to the group, the injection of per os lithium carboxylic intact animal

The glomerulus, the filtering unit of the kidneys, is a unique bundle of capillaries lined with delicate fenestrated endothelium, acomplex mesh of proteins that serve as glomerular basal membrane and specialized visceral epithelial cells [17]. The glomerulus is a unique structure required to filter blood while retaining plasma proteins, depending on size and charge selectivity. Individual cell types form a structural unit that creates a filtration barrier [18]. The glomerular filtration barrier is a highly specialized filtration interface between blood and urine that is highly permeable to small to medium-sized plasma solutes [19].

The glomerulus has 3 resident cells, namely mesangial cells that produce a mesangial matrix, endothelial cells that line the glomerular capillaries and podocytes that cover the outer surface of the glomerular basal membrane. The parietal epithelial cells that line the Bowman capsule are not part of the glomerular bundle, but may play an important role in normal glomerular function [20].

Glomerular capillaries are lined with highly specialized fenestrated endothelium, which is primarily responsible for regulating high-flow filtration of liquid and small solutes. During filtration, plasma passes through the fenestrated endothelium and the basal membrane before it reaches the slit diaphragm, a specialized type of intercellular junction that connects adjacent podocytes [21].

The nephron consists of the renal glomerulus, the proximal tubule, the thin part of the Henle loop (thin descending and thin ascending knee), the thick ascending knee of the Henle loop, the removed tubule, and the collecting tube. The renal glomerulus is surrounded by a Bowman's capsule formed by a dense basement membrane and lined with a flat single-layer (parietal) epithelium. Inside the Bowman's capsule is a glomerulus of blood capillaries. The walls of the capillaries are lined with fenestrated endothelium with a diameter of fester more than 100 nm. The capillary endothelium is surrounded by athin basal membrane and those who prefer toother interest-bearing delays. Between the processes of the podocytes there are slit diaphragms of 50–60 nm in size, closed by a thin film. Electron-dense mesangial cells are also localized in the pericapillary space of the Bowman capsule [22].

Changes in glomerulus filtration can significantly affect the dynamics and functions of the Boumen capsule [23]. The process of glomerulus development consists off our stages of development: the stage oft hevesicle (V), the stage of the S-shaped body (S), the stage of the capillary loop (C) and the stage (M) [24].

The cells that give out the thick ascending knee of the Henle loop and the distal convoluted canal have a similar ultrastructure. These are cuboidal epithelial cells about 10 microns high. The base surface of these cells forms numerous deep folds in which large mitochondria are located, removed up to 4 microns. On the apical surface of epithelial cells of the distal honor of the nephron, there is no brush border (only individual low microwaves can be detected), which sharply distinguishes the ultrastructural organization of these cells from the curse of the proximal tubule. The distal canal continues with a connecting tubule opening into the

collecting tube. The cell population of the epithelium of collective tubes consists of two types of cells, naturally diverse in morphological organization: main and intercalary cells. More numerous basic cells that perform reabsorption of water and sodium have a close to cubic shape. B characterized by an electron-transparent cytoplasm, in which the mitochondria are randomly distributed. Through out the cytoplasm relative to the sting organelles. Intercalar cells involved in regulating the systemic acid-base balance have an osmophilic cytoplasm filled with a mass of electron-dense mitochondria. Cells of the proximal renal tubule are characterized by the predominant presence of a mass of microvilli (brush border) on their apical surface and membrane folds on the basal surface. These structures provide an increase in the cell surface area necessary for the localization of a huge number of membrane transport proteins. The apical region of the cytoplasm contains vacuoles of various sizes. Basal warehouses associated with numerous mitochondria. The height of the epithelial layer and brush border, the depth of basal folding, and the proportions of mitochondria vary depending on the segment of the proximal tubule [22]. The proximal section is approximately 40–50 % of the total length of the nephron. In juxtamedular nephrons, the thin section of the Henle loop is more developed [25]. After 30 days, a 29 % decrease in the thickness of the basal membrane (BM) of glomerular capillaries was observed in the structure of the renal corpuscle y of animals with tumor growth. BM of the proximal and distal tubules thinned by 18 % and 27 %, the number of cytopodia increased by 5 %, and the thickness of the cytopodia decreased by 14 %, the number of Fenestra in the endothelial cells of glomerular capillaries decreased by 22 % (Table 2, Fig. 3C, 3D).

In the structure of the glomerular capsule lumen was observed in the structure of the renal body of animals with tumor growth in the presence of lithium carbonate peros. BM proximal and distal tubules thinned by 9 % and 27 %, the number of cytopodia increased by 4 %, and the thickness of the cytopodi are covered, the indicator is the sameas they group of control, the number of Fenestrain glomerular capillary endotheliocytes decreased by 46 % (Table 2, Fig. 3E, 3F).

In intact groups of animals that were given lithium carbonate, the values of the basal membrane of the proximal and distal tubule decreased by 9 % and 18 %, the number of cytopodia decreased by 17 %, and the thickness of the cytopodia increased by 11 %, the number of Fenestrain the endotheliocytes of glomerular capillaries decreased by 21 % (Tab. 2, Fig. 3G, 3H).

Table 2

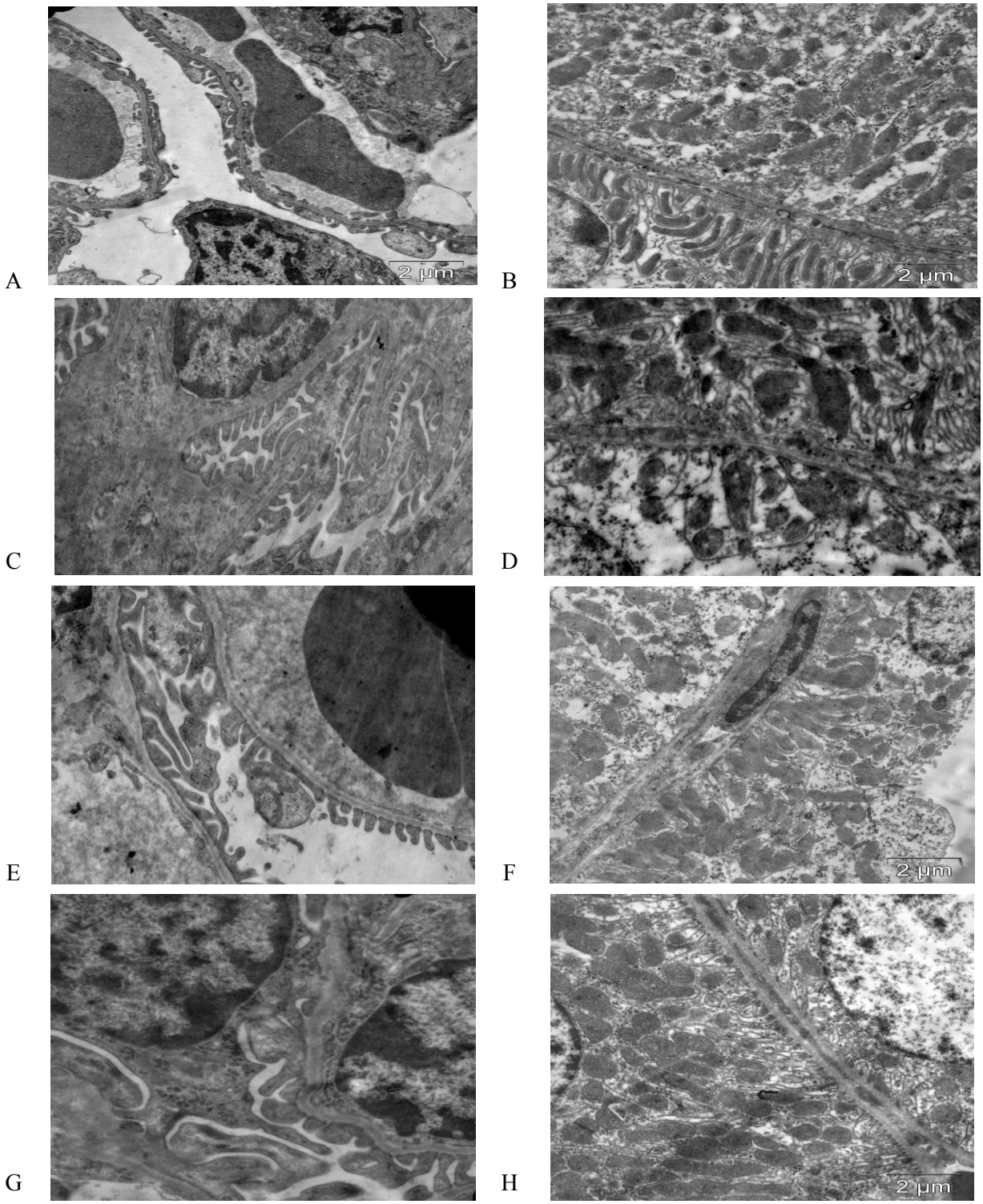
Results of morphometric study of structural components of nephron in CBA mice

Characteristics	Groups (M±SD)			
	Control	30 days KT	30 days TLC	30 days LC
BM of glomerular capillaries (μm)	0.14±0.03	0.10±0.02	0.14±0.03	0.14±0.06
The number podocyte (n)	6.91±2.36	7.25±3.19	7.2±2.48	5.73±2.37
Thickness of podocyte (microns)	0.36±0.28	0.31±0.26	0.36±0.31	0.40±0.34
Fenestra of glomerular capillary endotheliocytes (n)	5.25±3.15	4.11±2.17	2.82±1.43	4.16±2.19
BM of the proximal tubule (microns)	0.11±0.02	0.09±0.03	0.10±0.03	0.10±0.05
BM of the distal tubule (μm)	0.11±0.0492	0.08±0.02	0.08±0.02	0.09±0.03

Note: the Number podocyte and fenestra sendothelial cells of the glomerular capillaries is calculated by 11.2 μm test line.

Thus, distant tumor growth affects the structural organization of the kidneys. Injection of lithium carbonate tointact animals and animal tumour carriers causes opposite effects. Lithium carbonate does not have acorrective effect on the structure of the kidneys in the conditions of distant tumor growth.

Oral administration of lithium carbonate leads toan increase in the volume densities of the capsule lumen and toa decrease in glomerular capillaries and intercellular spaces.



Ultra-structure of the renal glomerulus and proximal tubule: *A, B* — control; *C, D* — after 30 days of tumor development; *E, F* — management of lithium carbonate per os animals with tumor growth; *G, H* — administration of lithium carbonate per os intact animals. Deep basal folds associated with large elongated mitochondria are observed

Figure 3. Structure of the renal corpuscle of mice of the CBA line of the control group

Conclusion

In the conditions of modeling of distant tumor growth — with the development of hepatocarcinomain the muscle tissue of the femur of experimental animals, morphological changes develop in the kidneys. There is an increase in the size of the lumen of the capsule and interstitial spaces of the renal body and a

decrease in the volume density of the capillary glomeruli. With the introduction of per os lithium carbonate, the size of the lumen of the renal cell capsule decreases, the volume density of the capillary glomeruliand the size of the interstitial spaces of the renal body increase. With the introduction of lithium carbonate per os lithium carbonate intact animals in the structure of the kidney noted an increase in the size of the lumen of the capsule of the renal corpuscle and a decrease in the volume density of capillary glomeruliand the size of interstitial spaces of the renal corpuscle. The use of lithium carbonate as an antitumor agent led toaggravation of structural changes in the kidneys, which, apparently, was due toan increase in toxic load.

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Қашықтықтағы ісіктің өсу жағдайында бүйрек құрылымына литий карбонатының әсері

Экспериментте СВА желілі тышқандарындағы литий карбонатының бүйрек құрылымына әсері зерттелген, яғни ісікке қарсы агент ретінде қолданылған. Гепатокарцинома-29 жасушаларын енгізу арқылы СВА желілі тышқандардың жамбас бұлшық еттеріне егіп, ісіктің өсуін модельдеген. Литий карбонаты жануарларға per os арқылы енгізілді. Бүйрек құрылымын жарық, электрондық микроскопия және морфометрия әдістерімен 30 тәуліктен кейін зерттелді. Бүйректердегі қашықтықтағы ісіктің өсу динамикасында ағза қызметінің бұзылғанын растайтын құрылымдық өзгерістер анықталған. Ісік дамуының 30-шы күніне қарай бүйрек денешігінің саңылау капсуласының мөлшерінің азаюы, қылтамырлардың көлемдік тығыздығының артуы, бүйрек денешігінің интерстициальдық кеңістігінің мөлшерінің артуы анықталды. Подоциттердің цитоплазмасының ісінуі, цитоподиялар санының артуы, қылтамырлар эндотелиоциттеріндегі фенестр санының төмендеуі, бүйректің проксимальды және дистальды бөлігінің эпителиоциттерінің ісінуі, сондай-ақ дистальды және проксимальды каналдардың базальды мембраналарының қалындығының азаюы байқалды. Литий карбонатын ісікке қарсы агент ретінде пайдалану бүйректердегі құрылымдық өзгерістердің ушығуына алып келді, бұл шамасы, литий әсерімен ісік жасушаларының ыдырауы мен өлуі өнімдерінің ұлғаюына байланысты ағзаға уытты жүктеменің өсуіне себепші болды.

Кілт сөздер: литий карбонаты, гепатокарцинома-29, бүйрек, бүйректің сүзу бөгеті, ультрақұрылым.

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Влияние карбоната лития на структуру почки в условиях отдаленного опухолевого роста

В эксперименте на мышах линии СВА изучали влияние карбоната лития на структуру почек, при его использовании как противоопухолевого агента. Моделировали опухолевый рост путем введения клеток гепатокарциномы-29 в мышечную ткань правого бедра экспериментальных животных. Карбонат лития вводили животным per os. Структуру почек изучали методами световой, электронной микроскопии и морфометрии через 30 сут эксперимента. В динамике отдаленного опухолевого роста в почках выявлены структурные изменения, свидетельствующие о нарушении функции органа. Показано, что к 30-м суткам развития опухоли происходит снижение размеров просвета капсулы почечного тельца, увеличение объемной плотности капиллярных клубочков, увеличение размеров интерстициальных пространств почечного тельца. Отмечали набухание цитоплазмы подоцитов, увеличение количества цитоподий, снижение количества фенестр в эндотелиоцитах клубочковых капилляров, набухание эпителиоцитов проксимального и дистального отдела почки, а также уменьшение толщины базальных мембран дистальных и проксимальных канальцев. Использование карбоната лития как противоопухолевого агента привело к усугублению структурных изменений в почках, что, по-видимому, было обусловлено возрастанием токсичной нагрузки на орган в связи с увеличением продуктов распада и гибели опухолевых клеток под влиянием лития.

Ключевые слова: карбонат лития, гепатокарцинома-29, почка, фильтрационный барьер почек, ультраструктура.

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