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Ultrastructure of the muscular membrane of the mice gallbladder wall under the influence of ursodeoxycholic acid

Abstract. Background. The aim of the research was to determine the ultrastructure of the cells of the muscle wall of the mice gallbladder under the influence of ursodeoxycholic acid. **Materials and methods.** The animals were divided into 2 groups: experimental ($n = 17$) — mice which received ursodeoxycholic acid at a dose of 100.0 mg/kg and control ($n = 13$) — intact ones (distilled water). Histological and ultrastructural analyses of gallbladder wall samples of mice were performed. **Results.** Mitotic figures of myocytes in the wall of the gallbladder bottom (1.794 ± 0.103 %) and body (1.607 ± 0.095 %) in the experimental group of mice were significantly more frequent compared to the controls (0.946 ± 0.058 % and 0.873 ± 0.061 %) ($p < 0.01$). Enhancing nuclear activity of fibroblasts due to chromatin decondensation and an increase in the number of nuclear pores were observed after the action of ursodeoxycholic acid (0.106 ± 0.007 vs. 0.253 ± 0.018) ($p < 0.01$). A considerable increase in the number of interstitial cells of Cajal in the muscular membrane of the bottom and body of the gallbladder was noted after the injection of ursodeoxycholic acid ($4.61 \pm 0.37 \text{ mm}^{-2}$ vs. $2.77 \pm 0.23 \text{ mm}^{-2}$) ($p < 0.01$). **Conclusions.** Our hypothesis was confirmed by the presence of histological signs of leiomyocyte hyperplasia and an increase in the nuclear activity of fibroblasts in the muscle wall of the mice gallbladder as a result of ursodeoxycholic acid use. Excessive activation of hyperplastic processes of leiomyocytes has an unsettled nature after the injection of ursodeoxycholic acid. An increase in apoptosis of smooth myocytes is observed under the influence of ursodeoxycholic acid. Stimulation of gallbladder wall motility with ursodeoxycholic acid might be associated with an increase in the number of interstitial cells of Cajal in the muscular membrane of the bottom and body of the gallbladder.

Keywords: ultrastructure; gallbladder; mice; leiomyocytes; fibroblasts; interstitial cells of Cajal; ursodeoxycholic acid

Introduction

Today, high efficiency of ursodeoxycholic acid (UDCA) has been proven in the treatment of hepatobiliary diseases [1–3]. A positive therapeutic effect of ursodeoxycholic acid drugs in these pathologies is due to hepatoprotective, choleric, litholytic, antifibrotic, antiapoptotic, cytoprotective and immunomodulatory effects [4, 5]. Treatment with ursodeoxycholic acid helps increase the gallbladder contractility in functional disorders of the gallbladder and sphincter of Oddi in children in our own clinical studies [6–8].

The scientists' works confirm the impact of UDCA therapy on the change in the expression of some microRNA which are used to treat various biliary diseases [9–11].

MicroRNAs are epigenetic factors regulating gene expression at the posttranscriptional level. MicroRNAs are used as highly sensitive, specific diagnostic and prognostic markers in modern diagnosis of biliary diseases [12–16]. Our clinical studies have found that ursodeoxycholic acid can affect the generation activity of microRNA. Increasing expression of micro-RNA-378f in the children's serum was observed in our studies during treatment for the functional disorders of the gallbladder and sphincter of Oddi after using ursodeoxycholic acid [17]. The system that allows you to regulate the fibroblasts transition to leiomyocytes is a system that gives an opportunity to fine-tune the number of smooth myocytes depending on apoptosis, damage, and the need for their

functioning. Experimental studies have confirmed that the expression of microRNA-378 is increased during skeletal muscle differentiation [18].

Therefore, taking into account the information mentioned above and the results of our own research, we suggested a hypothesis to increase the fibroblasts differentiation into smooth muscle cells of the gallbladder wall under the influence of ursodeoxycholic acid in an experimental model of mice. So, as UDCA has a positive effect on the contractile function of the children's gallbladder, we believe that this is the result of increased expression of microRNA-378f and hyperplasia of smooth myocytes in the gallbladder wall.

The aim of this work was to determine the ultrastructure of muscle cell membrane of the gallbladder wall in experimental mice under the influence of ursodeoxycholic acid.

Materials and methods

The experimental research was undertaken on 30 mice of the BALB/c line (weighing 20.0 ± 4.0 g at the beginning of the experiment). Mice undergone previous acclimatization for 14 days. They were kept in accordance with the sanitary and hygienic norms of the vivarium of the State Institution "Dnipropetrovsk Medical Academy of the Ministry of Health of Ukraine" (air temperature: 22 ± 2 °C, light/dark cycle: 12/12 h, food and drink *ad libitum*). All animals were examined by a qualified veterinarian before the research. Randomization in the group was carried out by the method of minimizing weight differences. During the experiment, the drug ursodeoxycholic acid (oral suspension, 50.0 mg/ml and 200.0 ml in vials) were used. Composition: 5.0 ml of suspension contains ursodeoxycholic acid 250.0 mg. By means of simple randomization, the animals were divided into 2 groups: experimental ($n = 17$) — mice which received ursodeoxycholic acid at a dose of 100.0 mg/kg and control ($n = 13$) — intact ones (distilled water). Distilled water and the study drug were administered intragastrically once daily for 30 days. At day 31, mice were sacrificed by cervical dislocation.

Samples of the mice gallbladder were fixed in Bouin's fluid. They were processed in ascending ethanol concentration and paraplast blocks were made according to standard methods. Tissue sections 3–5 μ m thick were stained with hematoxylin and eosin. Generally accepted standards of histological procedures were used [19]. Hematoxylin-eosin staining was performed to study the main structures which were part of the gallbladder wall. The dewaxed sections were placed in Heidenhain's hematoxylin solution (0.5 g of hematoxylin in 10.0 ml of ethanol and 90.0 ml of distilled water) for 15 minutes at room temperature followed by rinsing under running water for 5 minutes. After that, staining was carried out with 0.1% aqueous solution of eosin for 1 minute and inference procedure in the balm.

For ultrastructural analysis, mouse gallbladder samples were fixed at +2 °C for 2 hours in a 2.5% solution of glutaraldehyde prepared on 0.2 M phosphate buffer (pH 7.4). The material was transferred for post-fixation in a 1% buffered (pH 7.4) osmium tetroxide solution (SPI, USA) for 1 hour. The samples were dehydrated with propylene oxide in solutions of increasing concentration. Epon-araldite

composition was used to make epoxy blocks. Semi-thin sections 1 μ m thick were stained with methylene blue and basic magenta. During electron microscopic examination, the fabrication of ultrathin sections was performed on an ultramicrotome UMTP-6M. The sections were contrasted according to Reynolds at room temperature for 30 minutes. The study was performed using a transmission electron microscope PEM-100-01 at an acceleration voltage of 65–90 kV and primary magnifications from 3,000 to 15,000. In general, electron microscopy was used according to a standard scheme [20].

The experimental study had permission from the commission on biomedical ethics of the State Institution "Dnipropetrovsk Medical Academy of the Ministry of Health of Ukraine" (Minutes No. 6 dated October 4, 2019). The research was undertaken in accordance with the legislation of Ukraine in compliance with the relevant rules of ICH/GLP (Law of Ukraine No. 3447-IV "On protection of animals from cruel treatment"), the rules of the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes [21, 22].

Statistical analysis of our findings was performed using the program Statistica 6.1 (No. AGAR909E415822FA). Parametric and nonparametric statistical methods were used depending on the tests results. Differences between traits were considered statistically significant at $p < 0.01$.

Results and discussion

Light optical microscopy showed a loose reticular arrangement of smooth myocytes (leiomyocytes) in the muscular membrane of the animals' gallbladder wall in both study groups. Such cell structure is not characteristic of the walls of most tubular organs of the digestive system. The cell sizes of animals in both groups were 15–25 μ m in length and 3–7 μ m in diameter. The cells were elongated and spindle-shaped with single processes. The wall of the bottom and body of the gallbladder was represented by longitudinally and obliquely oriented myocytes and considerable layers of endomysium with a great number of microvascular and nerve elements (Fig. 1).

The wall of the gallbladder neck consisted of circularly oriented leiomyocytes which were tightly packed to each other (Fig. 2).

Signs of leiomyocyte hyperplasia of the gallbladder wall were histologically detected after exposure to ursodeoxycholic acid. Mitotic figures of myocytes of the bottom wall and gallbladder body in the experimental group of mice were significantly more frequent compared to the controls ($p < 0.01$). A great number of apoptotic figures of myocytes in the bottom wall and body of the gallbladder was probably observed in the experimental group of mice ($p < 0.01$) (Table 1).

From our point of view, unsettled excessive activation of hyperplastic processes which normally occurs with the introduction of ursodeoxycholic acid can cause activation of apoptosis of smooth myocytes of the bottom and body of the mice gallbladder.

The typical ultrastructural pattern of the cytoplasm, nuclei, and cell surface of gallbladder leiomyocytes in both groups is shown in Fig. 3.

Myocytes of all parts of the gallbladder contained an active nucleus with a predominance of decondensed chromatin, developed nucleoli of normal structure, a moderate number of nucleus pores and a solid nucleus membrane. Morphological signs of nuclei activity of interphase myocytes did not differ in the groups. General-purpose organelles also had a typical structure and localization in the myocyte cytoplasm.

Small mitochondria were located near the nucleus. The specific surface area of mitochondrial cristae and the density of the mitochondrial matrix of mice after exposure to ursodeoxycholic acid probably exceeded the indicators of

the control group of animals ($p < 0.01$) (Table 2). Agranular endoplasmic reticulum was moderately developed, and free ribosomes equally filled the cytoplasm. Elements of the lamellar complex, small lipid and carbohydrate inclusions were also found around the nucleus. As a result, according to these features, leiomyocytes of the experimental and control groups did not differ from each other. There was a significant increase in the number of caveolae on the plasmalemma surface and an increase in the saturation of the cytoplasm with micropinocytic vesicles after the injection of ursodeoxycholic acid ($p < 0.01$) (Fig. 4, Table 2). Certain changes in the mitochondria and surface apparatus of

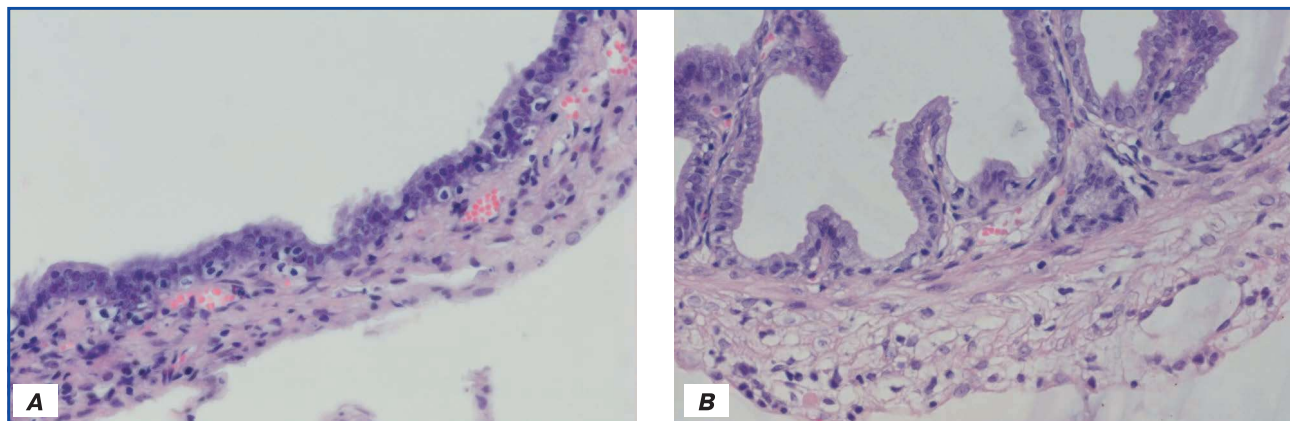


Figure 1. Histological microphotography of the wall of the bottom and body of the mouse gallbladder in the experimental (A) and control groups (B). Hematoxylin and eosin staining, $\times 400$

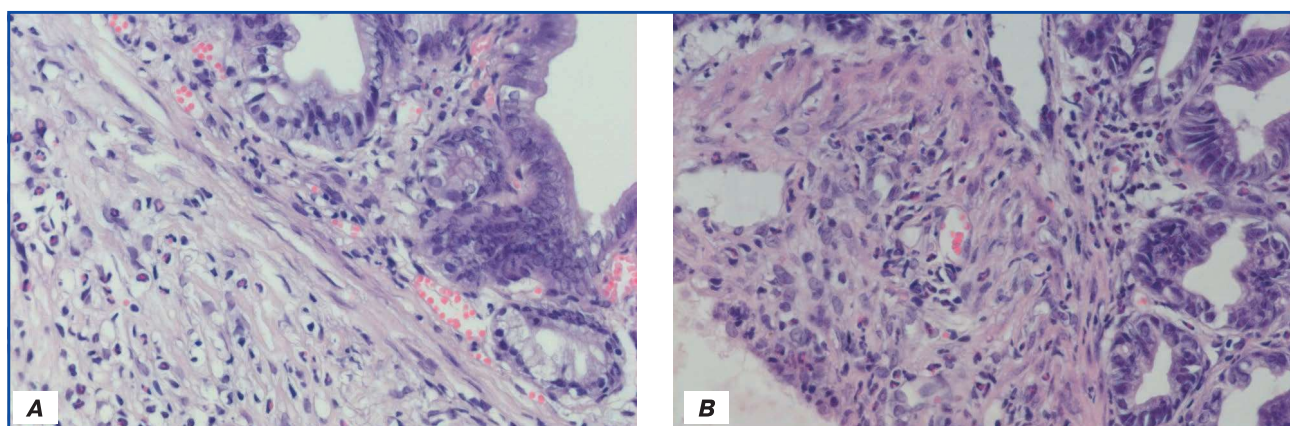


Figure 2. Histological microphotography of the wall of the neck of the mouse gallbladder in the experimental (A) and control groups (B). Hematoxylin and eosin staining, $\times 400$

Table 1. Mitotic and apoptotic indexes of leiomyocytes of the mice gallbladder wall under the influence of ursodeoxycholic acid ($M \pm m$)

Group of mice	Part of the gallbladder		
	Bottom	Body	Neck
<i>Mitotic index of leiomyocytes, %</i>			
Experimental (n = 17)	1.794 \pm 0.103*	1.607 \pm 0.095*	0.715 \pm 0.068
Control (n = 13)	0.946 \pm 0.058	0.873 \pm 0.061	0.659 \pm 0.043
<i>Apoptotic index of leiomyocytes, %</i>			
Experimental (n = 17)	0.762 \pm 0.046*	0.598 \pm 0.038*	0.165 \pm 0.015
Control (n = 13)	0.225 \pm 0.016	0.247 \pm 0.021	0.143 \pm 0.012

Note (here and in Tables 2–4): * – $p < 0.01$ – possible difference between the values of the experimental and control groups.

leiomyocytes due to the influence of ursodeoxycholic acid were observed within the bottom and body of the organ. The changes were not characteristic of the muscular membrane of the gallbladder wall.

These possible changes in mitochondria and leiomyocyte surface structures are directly related to the transport of

calcium ions into the myocytes cytoplasm for initiating the contraction. This indicates the stimulation of the contractile activity of leiomyocytes by means of ursodeoxycholic acid.

Bunches of actin filaments were presented by contractile myocytes structures. Bundles of actin filaments were located longitudinally or obliquely relative to the long axis of the

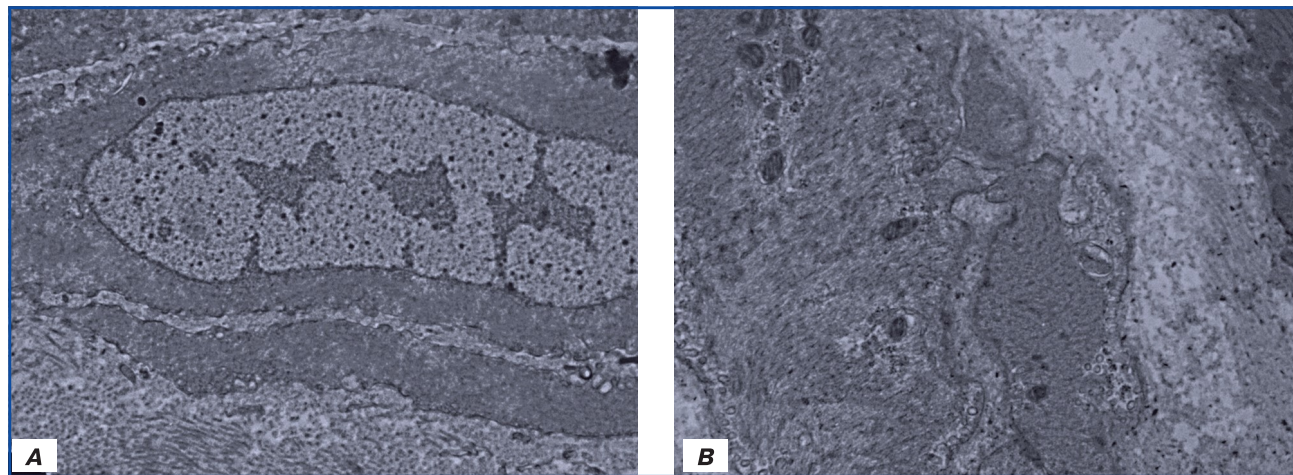


Figure 3. Electron micrograph of a leiomyocyte fragment of the muscular membrane of the wall of mouse gallbladder body in the experimental, $\times 12,000$ (A), and control groups, $\times 10,000$ (B)

Table 2. Ultrastructural characteristics of leiomyocytes of the mice gallbladder wall under the influence of ursodeoxycholic acid ($M \pm m$)

Group of mice	Part of the gallbladder		
	Bottom	Body	Neck
<i>Specific surface area of mitochondrial leiomyocyte cristae, $\mu\text{m}/\mu\text{m}^2$</i>			
Experimental (n = 17)	$5.32 \pm 0.39^*$	$3.85 \pm 0.31^*$	2.84 ± 0.23
Control (n = 13)	2.04 ± 0.15	1.43 ± 0.12	2.25 ± 0.16
<i>Specific number of caveolae of the outer membrane of leiomyocytes, μm^{-1}</i>			
Experimental (n = 17)	$67.6 \pm 4.9^*$	$44.1 \pm 3.5^*$	27.3 ± 2.3
Control (n = 13)	23.5 ± 2.1	13.9 ± 1.5	21.4 ± 1.7
<i>Numerical density of micropinocytic vesicles of leiomyocyte cytoplasm, μm^{-2}</i>			
Experimental (n = 17)	26.7 ± 2.3	$46.1 \pm 3.6^*$	13.8 ± 1.6
Control (n = 13)	22.4 ± 2.0	20.5 ± 1.8	10.7 ± 1.4

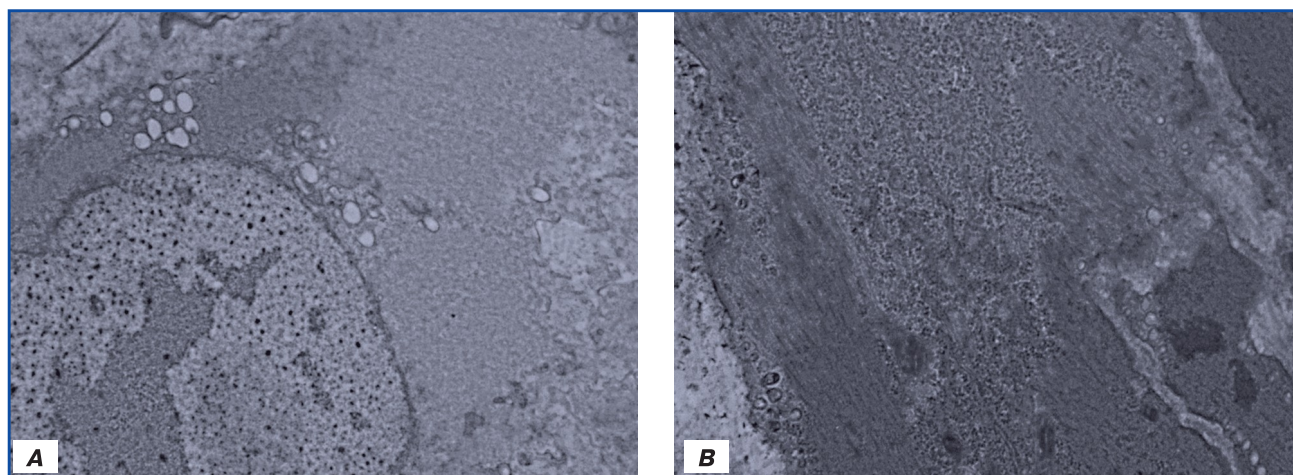


Figure 4. Electron micrograph of leiomyocyte cytoplasm of the muscular membrane of the bottom wall of the mouse gallbladder in the experimental, $\times 12,000$ (A), and control groups, $\times 10,000$ (B)

cells. The cytoplasm saturation with actin filaments was observed after exposure to ursodeoxycholic acid for 1 month.

Consequently, ultrastructural analysis of mouse muscle leiomyocytes revealed several important peculiarities. A possible difference between groups of animals was found after administration of ursodeoxycholic acid. Muscle hypertrophy in the experimental group due to smooth myocyte hyperplasia and numerous apoptosis occurred not at the tissue, but at the intracellular level. The mice muscle hypertrophy in the experimental group was due to an increase in the content and activity of the contractile elements and leiomyocytes energy apparatus and the calcium ions transport as well.

Numerous interstitial cells in the developed endomysium were found as a part of the muscular membrane of the gallbladder wall. They varied in shape, size, and intracellular ultrastructural features.

According to the results of electron microscopy, normal spindle-shaped fibroblasts with a small number of processes appeared to have the loosely located myocytes in both groups of animals. Fibroblasts are surrounded by elastic and thin collagen fibers which did not form organized bundles (Fig. 5). In the gallbladder neck, the layers of endomysium were much narrower and contained denser fibrils.

A growth in the nuclear activity of fibroblasts due to chromatin decondensation and an increase in the number of nucleus pores was observed under the influence of ursodeoxycholic acid ($p < 0.01$) (Table 3).

Active restructuring of endomysium was observed in the gallbladder muscle in the experimental group. This is confirmed by the presence of immature collagen fibrils alongside with the usual striped fibers. We believe that this was due

to parallel hyperplastic and apoptotic processes in muscular membrane of the gallbladder which occurred under the influence of ursodeoxycholic acid. The processes mentioned above required accelerated transformations of the interstitium.

The heteromorphic interstitial cells of Cajal (telocytes) were found in the endomysium in both study groups. The bodies of Cajal cells varied in size from 8 to 30 μm . The telocytes contained from 2 to 8 processes and often had branches (Fig. 6). The presence of numerous contacts of the processes with the membrane of neighboring leiomyocytes was the characteristic feature of interstitial cells of Cajal. Some telocytes with 2–3 processes were located along the nerve fibers or in contact with the nerve endings in the thickness of the endomysium.

A substantial increase in the number of interstitial cells of Cajal in the muscular membrane of the bottom and body of the mice gallbladder was revealed after the injection of ursodeoxycholic acid ($p < 0.01$). These changes did not occur in the sphincter of the gallbladder (Table 4).

Ultrastructural signs of nuclear and cytoplasmic activity of interstitial cells of Cajal did not differ from those in the control group of animals. We did not notice any changes in the structure of contacts of telocytes with leiomyocytes or nerve elements. We assume that an increase in telocytes density in the muscle membrane stimulates the motility of the gallbladder wall. Taking into consideration a modern concept about the pacemaker role of interstitial cells of Cajal in initiating the contraction of smooth muscle complexes, it can be assumed that an important mechanism of ursodeoxycholic acid action is stimulation of the gallbladder wall motility.

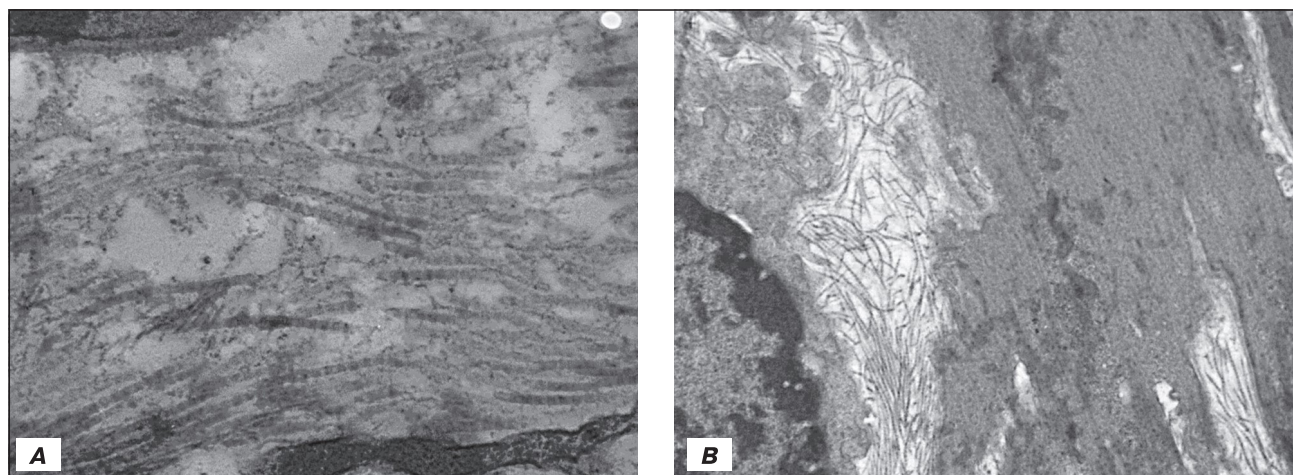


Figure 5. Electronic microphotography of the collagen matrix in the endomysia of the muscular membrane of the visceral wall of the mouse gallbladder body in the experimental, $\times 25,000$ (A), and control groups, $\times 15,000$ (B)

Table 3. The ratio of condensed and decondensed chromatin of the nuclei of fibroblasts in the muscular membrane of the mice gallbladder after the injection of ursodeoxycholic acid ($M \pm m$)

Group of mice	Part of the gallbladder		
	Bottom	Body	Neck
Experimental (n = 17)	0.106 \pm 0.007*	0.121 \pm 0.009*	0.094 \pm 0.008*
Control (n = 13)	0.253 \pm 0.018	0.195 \pm 0.016	0.206 \pm 0.015

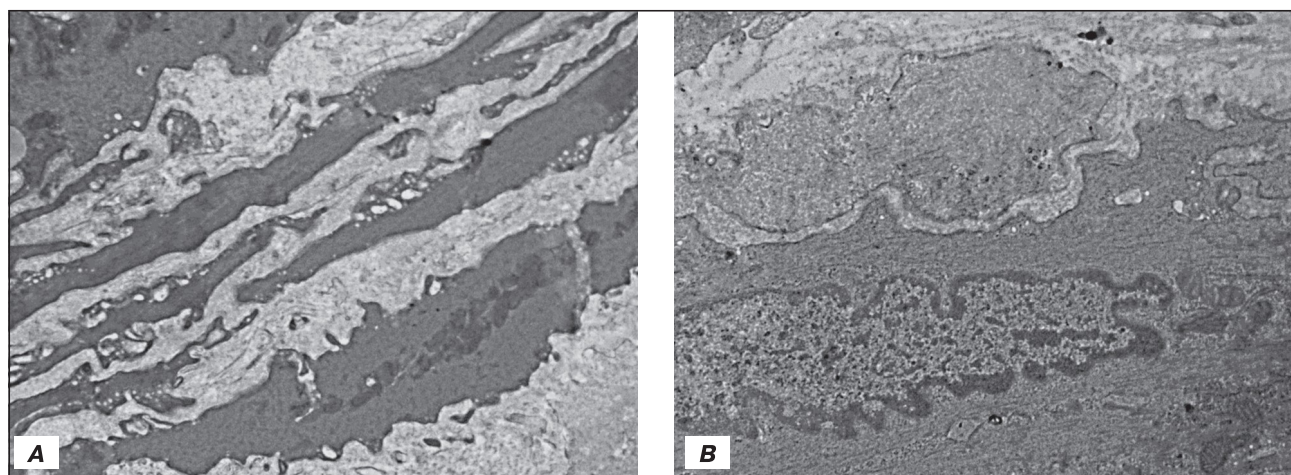


Figure 6. Electron micrograph of endomyia interstitial cells of the muscular wall of the gallbladder in the experimental, $\times 4,000$ (A), and control groups, $\times 8,000$ (B)

Table 4. Numeral density of telocytes in the muscular membrane of the mice gallbladder under the influence of ursodeoxycholic acid ($M \pm m$), mm^{-2}

Group of mice	Part of the gallbladder		
	Bottom	Body	Neck
Experimental (n = 17)	4.61 \pm 0.37*	5.48 \pm 0.40*	1.98 \pm 0.17
Control (n = 13)	2.77 \pm 0.23	2.06 \pm 0.19	1.84 \pm 0.14

Conclusions

Thus, an introduced hypothesis was confirmed by the existence of histological signs of leiomyocyte hyperplasia and an increase in the nuclear activity of the muscular wall fibroblasts in the mice gallbladder under the influence of ursodeoxycholic acid. Excessive activation of hyperplastic processes in leiomyocytes has an unsettled nature after the injection of ursodeoxycholic acid. There was also an increase in apoptosis of smooth myocytes, the content and activity of elements of the contractile and energy apparatus of leiomyocytes, in the transport of calcium ions indicating the stimulation of the contractile activity of gallbladder leiomyocytes at the intracellular level. A considerable growth in the number of interstitial cells of Cajal in the muscular membrane of the bottom and body of the gallbladder is observed after the injection of ursodeoxycholic acid. Stimulation of gallbladder wall motility with ursodeoxycholic acid might be associated with an increase in the number of interstitial cells of Cajal in the muscular membrane of the bottom and body of the gallbladder.

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Ультраструктура м'язової оболонки стінки жовчного міхура мишей під впливом урсодезоксихолевої кислоти

Резюме. Актуальність. Метою дослідження стало визначення ультраструктури клітин м'язової оболонки стінки жовчного міхура мишей при використанні урсодезоксихолевої кислоти. **Матеріали та методи.** Методом простої рандомізації тварини були розподілені на 2 групи: експериментальну (n = 17) — миші, які отримували урсодезоксихолеву кислоту в дозі 100,0 мг/кг, та контрольну (n = 13) — інтактні тварини (дистильована вода). Проведено гістологічний та ультраструктурний аналіз зразків стінки жовчного міхура мишей. **Результати.** Мітотичні фігури міоцитів стінки дна (1,794 ± 0,103 %) та тіла (1,607 ± 0,095 %) жовчного міхура в експериментальній групі виявлялися вірогідно частіше порівняно з контрольною групою мишей (0,946 ± 0,058 % та 0,873 ± 0,061 %) (p < 0,01). Кількість мітохондріальних крист (5,32 ± 0,39 мкм/мкм²) після введення урсодезоксихолевої кислоти вірогідно перевищувала таку в контрольній групі (2,04 ± 0,15 мкм/мкм²) (p < 0,01). Зростання ядерної активності фібробластів за рахунок деконденсації хроматину та збільшення частки ядерних пор спостерігалось під впливом урсодезоксихолевої кислоти

(0,106 ± 0,007 проти 0,253 ± 0,018; p < 0,01). Суттєве збільшення кількості інтерстиціальних клітин Кахалія в м'язовій оболонці дна та тіла жовчного міхура зареєстровано після використання урсодезоксихолевої кислоти (4,61 ± 0,37 мм⁻² проти 2,77 ± 0,23 мм⁻²) (p < 0,01). **Висновки.** Запропонована нами гіпотеза підтверджена наявністю гістологічних ознак гіперплазії лейоміоцитів та зростанням ядерної активності фібробластів у м'язовій оболонці стінки жовчного міхура мишей після дії урсодезоксихолевої кислоти. Надлишкова активація гіперпластичних процесів у лейоміоцитах має нерегульований характер при введенні урсодезоксихолевої кислоти. Підсилення апоптозу гладких міоцитів спостерігається після застосування урсодезоксихолевої кислоти. Стимуляція моторики жовчного міхура за допомогою урсодезоксихолевої кислоти може бути пов'язана зі збільшенням кількості інтерстиціальних клітин Кахалія у м'язовій оболонці дна та тіла жовчного міхура.

Ключові слова: ультраструктура; жовчний міхур; миші; лейоміоцити; фібробласти; клітини Кахалія; урсодезоксихолева кислота