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# Ultrastructural changes of hemocapillaries of the lungs in the late development of experimental acute pancreatitis

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**Abstract**

**Background**. Today, acute pancreatitis is a common form of acute abdomen in the clinic, the incidence of which has been increasing in recent years. **The aim of the work** was to study the dynamics of ultrastructural changes of the hemocapillaries of the alveolar wall of the lungs in the late stages of experimental acute pancreatitis. **Material and methods.** The experiments were carried out on 54 white Wistar male rats weighing 180–220 g. The animals were divided into three groups: first — intact, second — control, third — experimental with a model of acute pancreatitis, which was reproduced by intraperitoneal administration of a 20% solution of L-arginine at a total dose of 5 g/kg at one-hour interval. The control group of animals was intraperitoneally injected with an equivalent dose of isotonic sodium chloride solution. All research were performed under sodium thiopental anesthesia at the rate of 60 mg/kg body weight. Lung tissue for electron microscopic examination was collected from the lower lobe of the left lung at 3–5 and 7 days. Pieces of lung tissue measuring 1×1×1 mm were fixed in a 2.5% glutaraldehyde solution, followed by additional fixation in a 1% osmium tetroxide solution. After dehydration, the material was poured into Epon-Araldite. Sections with a thickness of 20–50 nm obtained on "Tesla BS-490" ultramicrotome were studied in a PEM-125K electron microscope. **Results.** The ultrastructural analysis showed that already 3 days after the study, dystrophic-destructive changes, as well as adhesion and aggregation of leukocytes, were detected in the endothelial cells. As the study period increased (5–7 days), the intensity of changes in the hemocapillaries of the alveolar wall increased significantly. In the lumen erythrocyte sludge, thromboleukocyte adhesion and aggregation are determined in hemocapillaries. **Conclusion.** Acute experimental pancreatitis is accompanied by marked changes in the ultrastructural structure of hemocapillaries of the alveolar wall. The nature and severity of structural changes in the hemocapillaries of the alveolar wall depends on the duration of the course of arginine-induced acute pancreatitis.

**Key words**: arginine-induced acute pancreatitis, lungs, hemocapillaries of the alveolar wall.

## INTRODUCTION

Today, acute pancreatitis (AP) is a common form of acute abdomen in the clinic, the incidence of which has been increasing in recent years [2,7,9,10]. AP is a serious systemic inflammatory disease and often leads to distant organ dysfunction with high morbidity and mortality [1,8,11]. Acute lung injury is one of the most serious and earliest injuries of AP. It has been established that one of the main factors in the development of pulmonary complications in AP is angiopathy, which leads to impaired hemomicrocirculation [3,9,12].

The ultrastructural changes of hemocapillaries in the lungs during the late development of experimental acute pancreatitis have been a subject of interest in various studies. Experimental acute pancreatitis can lead to severe complications, including acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) [13]. These conditions are associated with high morbidity and mortality rates, making them crucial areas of research [14]. The lungs are particularly susceptible to the effects of severe acute pancreatitis, with the development of ALI being a significant concern [15]. Studies have explored different interventions to mitigate the impact of acute pancreatitis on the lungs. For instance, Emodin has been shown to alleviate severe acute pancreatitis-associated acute lung injury by inhibiting specific signaling pathways [16]. Similarly, Daphnetin has demonstrated efficacy in ameliorating acute lung injury in severe acute pancreatitis by modulating the JAK2–STAT3 pathway [17]. Sitagliptin has been found to activate signaling pathways that alleviate oxidative stress and excessive autophagy in severe acute pancreatitis-related acute lung injury [18]. The systemic effects of severe acute pancreatitis on distant organs, including the lungs, have been highlighted in research [14]. The role of neutrophilic granulocytes in the development of acute lung injury in experimental models has been investigated, emphasizing the importance of understanding the underlying mechanisms of organ cross-talk in disease progression [19]. The impact of intestinal microbiota on severe acute pancreatitis-associated acute lung injury has been explored, underscoring the interconnectedness of different organ systems in disease pathogenesis [20]. The studies reviewed shed light on the complex interplay between acute pancreatitis and lung complications. Understanding the ultrastructural changes in the lungs during the late development of experimental acute pancreatitis is crucial

for developing effective therapeutic strategies to mitigate lung injury in patients with severe acute pancreatitis.

**The aim of the work** was to study the dynamics of ultrastructural changes in the hemocapillaries of the alveolar wall of the lungs in the late stages of experimental acute pancreatitis (EAP).

## MATERIAL AND METHODS.

The experiments were carried out on 54 white Wistar male rats weighing 180–220 g. The animals were divided into three groups: first — intact, second — control, third — experimental with a model of acute pancreatitis, which was reproduced by intraperitoneal administration of a 20% solution of L-arginine at a total dose of 5 g/kg at one-hour interval. The control group of animals was intraperitoneally injected with an equivalent dose of isotonic sodium chloride solution. All research were performed under sodium thiopental anesthesia at the rate of 60 mg/kg body weight. Lung tissue for electron microscopic examination was collected from the lower lobe of the left lung at 3–5 and 7 days. Pieces of lung tissue measuring 1×1×1 mm were fixed in a 2.5% glutaraldehyde solution, followed by additional fixation in a 1% osmium tetroxide solution. After dehydration, the material was poured into Epon-Araldite. Sections with a thickness of 20–50 nm obtained on “Tesla BS-490” ultramicrotome were studied in a PEM-125K electron microscope.

## RESULTS AND DISCUSSION

The conducted ultrastructural analysis shows that in three days after the start of the study, nuclei of endothelial cells are enlarged in volume with nucleoplasm of low electron-optical density (Fig. 1).

An ultrastructural analysis performed 3 days after the study showed that the nuclei of endothelial cells were enlarged in volume and with a matrix of low electron-optical density.

The perinuclear space is expanded. The nucleolema has winding contours and forms shallow intussusceptions. Chromatin granules in many cells are located along the inner surface of the nucleolem. The Golgi apparatus (GA) is observed in the perinuclear area, represented by enlarged cisternae, small vesicles and vacuoles. Mitochondria are enlarged in

volume, of different sizes and shapes with individual disorganized cristae. A significant part of the tubules of the granular endoplasmic reticulum (GER) is expanded. The number of ribosomes on the outer surface of membranes is reduced. Pronounced phenomena of hyperhydration are determined in the peripheral sections of endothelial cells (Fig. 1) Adhesion and aggregation of leukocytes is detected in the lumen of hemocapillaries.

With the increase of the study period (5–7 days), the intensity of changes in the hemocapillaries of the alveolar wall increases significantly, compared to the previous study period. The nuclei of many endotheliocytes are enlarged with a lightened matrix and marginal aggregation of chromatin granules. The perinuclear lumen is widened. A significant part of mitochondria with a matrix of low electron-optical density and single disoriented cristae. There is also a partial destruction of mitochondria. GER cisternae are expanded with a reduced number of ribosomes on the membranes of the latter.

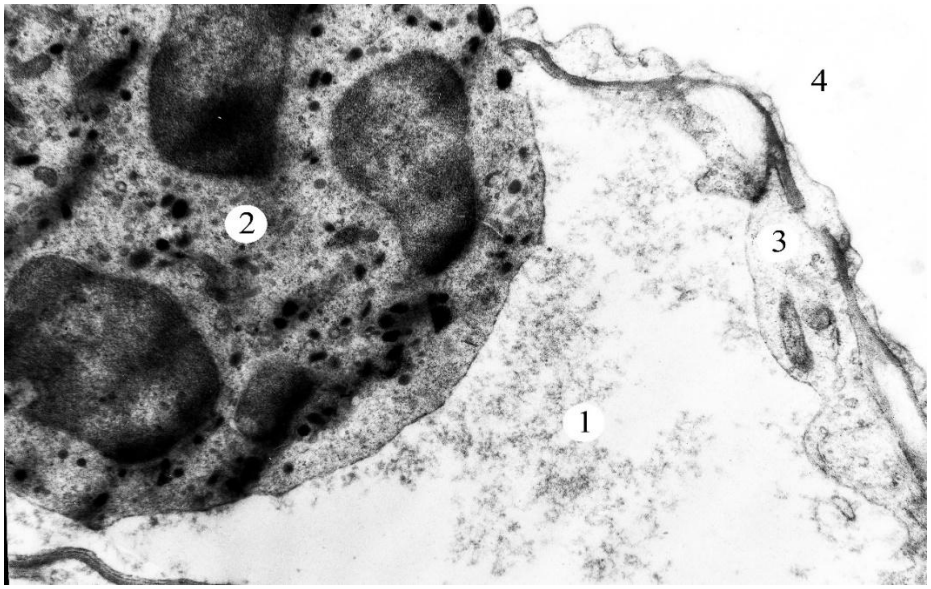


Figure 1. Ultrastructural changes of the hemocapillaries of the alveolar wall 3 days after the start of the experiment. Electron micrograph x 8000.

Key: 1 — hemocapillary lumen; 2 — leukocyte; 3 — peripheral part of endotheliocyte; 4 — alveolar lumen.

Along with this, the fragmentation of GER membranes is also revealed. GA is represented by vesicularly expanded cisterns and a small number of vesicles. Hyperhydration of endotheliocytes is accompanied by the rupture of the apical plasmolemma and the release

of cytoplasmic structures into the hemocapillary lumen. The basement membrane is thickened with indistinct contours. In the lumen of hemocapillaries, erythrocyte sludge, thromboleukocyte adhesion and aggregation are determined.

Electron microscopic studies have shown that in acute arginine-induced pancreatitis there are marked violations of the ultrastructural structure of the hemocapillaries of the alveolar wall. A number of other scientists point to changes of a similar nature under the action of exo- and endogenous factors [4,5,6].

The ultrastructural analysis conducted three days after the study initiation revealed that the nuclei of endothelial cells exhibited an increase in volume and a matrix with low electron-optical density. This observation aligns with findings from previous studies on various cell types, such as megakaryocytes, where enlarged nuclei with distinct characteristics were identified [21]. Different cell pathologies, including tumors and neoplasms, have reported similar features of enlarged nuclei with prominent nucleoli and altered chromatin patterns [22,23].

Endothelial cells in different contexts, such as in response to oxidative stress or during vascular development, have highlighted changes in cell morphology, including alterations in nucleus size and cellular orientation [24,25,26].

The enlargement of nuclei in endothelial cells can be indicative of various processes, such as cellular stress responses, pathological conditions, or developmental changes. For instance, in the context of brain vascular endothelial cells, changes in nucleus size have been associated with alterations in cellular permeability and tight junction integrity under pathological conditions [26]. Endothelial cells in the context of cardiovascular diseases have emphasized the role of oxidative stress in inducing cellular changes, including alterations in nucleus size and cellular migration [24]. These findings suggest that the observed enlargement of nuclei in endothelial cells may reflect underlying physiological or pathological processes affecting these cells.

The ultrastructural analysis revealing the enlargement of nuclei in endothelial cells after three days of the study provides valuable insights into the cellular changes occurring in response to the experimental conditions. By comparing these observations with findings from relevant studies on various cell types and pathologies, it is evident that changes in nucleus size and morphology are dynamic processes that can be influenced by a range of factors. Understanding the implications of these cellular changes in endothelial cells is crucial for elucidating their functional significance in different physiological and pathological contexts.

The observed changes in the hemocapillaries of the alveolar wall, including the expansion of the perinuclear space, alterations in nucleolema contours, changes in chromatin granule distribution, and modifications in organelles such as the Golgi apparatus, mitochondria, and granular endoplasmic reticulum, indicate significant cellular transformations over a 5-7 day period [27]. These changes involve the enlargement of nuclei, disorganization of mitochondria, expansion of GER cisternae, and reduced ribosome numbers on membranes [27]. Such alterations in cellular structures and organelles can have profound implications on cellular function and health.

The Golgi apparatus, a key organelle involved in protein processing and trafficking, plays a crucial role in cellular homeostasis and disease development [28,29,30]. Golgi apparatus abnormalities can lead to various diseases, including neurodegenerative disorders and autoimmune conditions [29]. Golgi apparatus is essential for maintaining cellular polarity, communication, and immune signaling [30]. Disruption of the Golgi apparatus has been linked to lysosomal dysfunction, emphasizing its significance in cellular processes [31].

Golgi apparatus serves as a target for drug delivery systems aimed at suppressing cancer metastasis and enhancing therapeutic outcomes [32,33]. Targeting the Golgi apparatus with fluorescent probes or nanovaccines can disrupt its function and potentially inhibit cancer progression [34,35]. Golgi apparatus is also involved in regulating immune responses, as seen in the trafficking of Toll-like receptors.

Observed cellular changes in the hemocapillaries reflect dynamic alterations in organelles like the Golgi apparatus, mitochondria, and endoplasmic reticulum, which can impact cellular function and health. Understanding the role of the Golgi apparatus in disease pathogenesis and drug targeting strategies highlights its significance in cellular biology and therapeutic interventions.

The ultrastructural changes observed in acute arginine-induced pancreatitis include disruptions in the hemocapillaries of the alveolar wall, such as endotheliocytes hyperhydration, apical plasmolemma rupture, and thickening of the basement membrane. These changes lead to the release of cytoplasmic structures into the hemocapillary lumen, erythrocyte sludge formation, and thromboleukocyte adhesion and aggregation. Additionally, the fragmentation of GER membranes is evident, with GA represented by vesicularly expanded cisterns and vesicles. These alterations are indicative of severe damage to the microvasculature and cellular structures in the pancreas under the influence of various factors [36].

The pathogenesis of severe acute pancreatitis involves critical disturbances in the blood coagulation system, emphasizing its role in the development of the condition [36]. The involvement of mitochondrial calcium uniporter in promoting mitophagy in pancreatic ductal epithelial cells under specific treatments highlights the intricate cellular responses in pancreatitis [37]. The dysregulation of autophagy pathways and the potential impact on cellular homeostasis are also suggested in the context of pancreatic acinar cells [38].

Pancreatic beta cell autophagy in type 1 diabetes underscores the importance of understanding cellular mechanisms in pancreatic diseases. The impaired autophagy in beta cells contributes to the pathophysiology of diabetes, indicating the significance of cellular processes in pancreatic health [39]. The intricate cellular responses and structural changes that occur in the pancreas under various pathological conditions, shedding light on the complexity of pancreatic diseases.

## CONCLUSION

Acute experimental pancreatitis is accompanied by pronounced changes in the ultrastructural structure of hemocapillaries of the alveolar wall. The nature and severity of structural changes in the hemocapillaries of the alveolar wall depends on the duration of the course of arginine-induced acute pancreatitis.

During acute experimental pancreatitis, there are significant alterations observed in the ultrastructural composition of the hemocapillaries within the alveolar wall. These changes in the hemocapillaries' structure can vary in nature and severity, depending on how long the arginine-induced acute pancreatitis lasts. The duration of the condition plays a crucial role in determining the extent of structural modifications in the hemocapillaries of the alveolar wall.

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