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R.S. Vastyanov, O.M. Stoyanov, S.V. Tertyshnyi, V.V. Babienko, O.A. Hruzevskiy, K.O. Talalayev, M.R. Vastianov
Odesa National Medical University, Odesa

IMPACT OF OCTREOTIDE ON LUNG RECOVERY IN ACUTE EXPERIMENTAL CAERULEIN-INDUCED PANCREATITIS

e-mail: rvastyanov@gmail.com

The purpose of the study was to provide the pathophysiological explanation of octreotide therapeutic effect on lung recovery in acute experimental pancreatitis. Experimental studies were performed on the model of caerulein-induced acute pancreatitis on Wistar rats which were injected with Octreotide. NaCl solution was used as a reference drug. The expression of lipoperoxidation and antioxidant defense together with pathomorphological changes in pancreas and lungs were determined during the 48 hrs of the trial. The inducible NO synthase activity, the content of tumor necrosis factor, interleukin-1 and intercellular adhesion molecule were determined in blood serum. The data obtained confirm the lipoperoxidation products accumulation, the antioxidant enzymes activity inhibition and pathomorphological changes in pancreatic and lungs cells of rats with caerulein-induced acute experimental pancreatitis. The inducible NO-synthase activation, the proinflammatory cytokines and intercellular adhesion molecules content increase is recorded in blood serum of rats with caerulein-induced acute experimental pancreatitis. The Octreotide injection causes the pneumoprotective efficacy which mechanisms of implementation involve its antiinflammatory, antioxidant and antihypoxic effects. The authors supposed the data obtained are the experimental evidence of Octreotide clinical efficacy testing reasonability to prevent lung damage in acute inflammatory lesions of the pancreas.

Key words: caerulein, rats, acute experimental pancreatitis, lungs, inflammation, NO synthase, cytokines, lipid peroxidation, antioxidant defense, octreotide, pathogenetic mechanisms.

Р.С. Вастьянов, О.М. Стоянов, С.В. Тертишний, В.В. Бабієнко, О.А. Грузевський, К.О. Талалаєв, М.Р. Вастьянов

ВПЛИВ ОКТРЕОТИДУ НА ВІДНОВЛЕННЯ ЛЕГЕНЬ ПРИ ГОСТРОМУ ЕКСПЕРИМЕНТАЛЬНОМУ ЦЕРУЛЕЇН-ІНДУКОВАНОМУ ПАНКРЕАТИТІ

Метою дослідження було патофізіологічне обгрунтування лікувального впливу октреотиду на відновлення легень за умов гострого експериментального панкреатиту. Експериментальні дослідження проводили на моделі церулеїн-індукованого гострого панкреатиту на щурах лінії Вістар, яким уводили октреотид. В якості референт-препарату застосовували розчин NaCl. Вираженість процесів ліпопероксидації та антиоксидантного захисту, а також патоморфологічні зміни в підшлунковій залозі та легенях визначали протягом 48 год досліду. В сироватці крові визначали активність індуцибельної NO-синтази, вміст фактору некрозу пухлини, інтерлейкіну-1 та міжклітинної молекули адгезії. Отримані дані свідчать про накопичення продуктів ліпопероксидації, пригнічення активності антиоксидантних ферментів, а також виражені патоморфологічні зрушення в клітинах підшлункової залози та легенів щурів із церулеїн-індукованим гострим експериментальним панкреатитом. В сироватці крові щурів із церулеїн-індукованим гострим експериментальним панкреатитом реєструється активація індуцибельної підтипу NO-синтази, зростає вміст прозапальних цитокінів та міжклітинної молекули адгезії. Введення октреотиду спричиняє розвиток пневмопротекторних ефектів, до механізмів реалізації яких залучені його протизапальні, антиоксидантні та антигіпоксичні ефекти. Отримані дані автори вважають експериментальним доказом доцільності тестування клінічної ефективності ОТ з метою попередження ураження легенів при гострому запальному ураженні підшлункової залози.

Ключові слова: церулеїн, щури, гострий експериментальний панкреатит, легені, запалення, NO-синтаза, цитокіни, перекисне окислення ліпідів, антиоксидантний захист, октреотид, патогенетичні механізми.

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Treatment of patients with acute pancreatic injuries of inflammatory genesis – acute pancreatitis, especially with its destructive forms, remains a complex and time-consuming problem of modern medicine confirmed by progressive increasing of incidence and high mortality rates together with frequencies of purulent-septic and other complications [10]. This current situation is apparently explained by this form of pancreatic damage pathogenesis complexity, by disease rapid progression to necrotic form development with quick and maximal mortality, by lack of early diagnosis and complications development [10, 14].

Pancreatic parenchyma acute inflammatory damage pathogenesis complexity and its rapid clinical progression cause complications or concomitant comorbid conditions in the form of systemic inflammatory response syndrome and internal organs damage such as acute lung injury or acute respiratory distress syndrome approximately in 20 % of patients [14]. Regulatory mechanisms complete failure together with immune system activity collapse is believed to be one of the leading mechanisms of such severe complications in acute pancreatitis development. Their pathophysiological mechanisms include systemic inflammatory, ischemic and hypoxic nature that stimulates the progressive organ failure, multi-cascade cytotoxic mechanisms based on positive feedback, etc. [11].

Internal organs and systems of the body dysfunction or pathological dysregulation takes place in this pathological condition of pancreatic parenchyma damage additionally to the expressed systemic inflammation in the body. All named above "launches" systemic disorders via the "vicious circle" mechanisms, positive feedback and systemic-antisystemic regulation. Fundamentally, peroxide mechanisms normally participated in the majority of regulatory conditions cannot be excluded from these obligatory chains of pathogenetic mechanisms responsible for all functional "breakdowns" and disorders [1]. Hence, we were interested in lipid peroxidation and antioxidant defense changes which manifestation in blood, in pancreatic and lungs tissue we supposed to be pathogenetically important in acute pancreatitis.

The mechanisms of lung damage in acute pancreatitis appear to ne insufficiently investigated despite the so-called acute pancreatitis diagnosis, treatment and complications prevention details explanation, and such a clinical fact appears unexpected while major contingent of patients with acute pancreatitis treatment [12]. That's why we provided experimental trials to determine the pathogenetic mechanisms of lung damage in pancreas acute inflammatory damage accenting attention to inflammatory and peroxide mechanisms.

Thinking about the pathogenetically oriented complexity of respiratory system pathology treatment in acute pancreatitis, we the efficacy of sandostatin peptide analogue octreotide (OT) which has therapeutic and prophylactic activity in acute pancreatitis due to its facility to inhibit the pancreatic enzymes secretion and to provide anti-inflammatory effects by signaling cascades modulation [2].

The purpose of the study was to provide the pathophysiological explanation of octreotide therapeutic effect on lung recovery in acute experimental pancreatitis.

Materials and methods. Experimental studies were performed on 97 white matured male Wistar rats. The animals were kept in individual boxes with 12 hrs of light and dark, humidity of 60 %, constant temperature of 22±1 ºC, with free access to water and food. Animal preparation, all interventions, anesthetics and withdrawal from the experiment were carried out in full compliance with the requirements of the Guidelines of the State Pharmacological Center of the Ministry of Health of Ukraine (Kyiv, 2001), as well as the GLP rules provided by the European Commission for the supervision of laboratory and other studies, in accordance with Code of Scientist of Ukraine.

Animal euthanasia was carried out in accordance with the provisions regulated by Annex 8 of the "Rules for the humane treatment of laboratory animals", "Sanitary rules for equipment, equipment and maintenance of experimental biological clinics (vivarium)" No 1045-73.

The following groups of experimental rats were used: 1 – control (intact animals, n=6); 2 – rats with acute experimental pancreatitis (AEP; n=7); 3 – rats with AEP which intraperitoneally (i.p.) received the reference drug 0.9 % saline NaCl solution (n=6); 4 – rats with AEP which received octreotide (i.p., Sadostatin, 50 µg/kg; "Novartis Pharma", Switzerland; n=6).

Acute experimental pancreatitis was induces by caerulein ("Sigma-Aldrich", Germany; 20 mg/kg) 4 i.p. injections with 1-hour intervals between each injection [4]. Control animals were injected with equal volumes of 0.9 % saline NaCl. After animals' euthanasia (at 12, 24, 36 and 48 hrs of the trial) by sodium etaminal overdose (i.p., 100 mg/kg), blood was collected, the pancreas and lungs were removed and a homogenate of these organs was prepared in 10 mM Tris-HCl buffer (pH=7.4) by centrifugation for 10 min at 3000 g (t=0±2 °C).

Malonic dialdehyde (MDA) and dienic conjugates (DC) concentrations together with the antioxidant enzymes – superoxidedismutase (SOD), catalase and glutathioneperoxidase (GTP) activities were determined in these organs supernatants according to described method [1].

The inducible NO synthase activity (spectrophotometrically) and cytokines – tumor necrosis factor-alpha (TNFα) and interleukin-1-beta (IL-1β) – concentration in blood serum were determined using the enzyme-linked immunosorbent assay (ELISA test). ELISA kits ("Biomedica Group", Austria) were used to detect the intercellular adhesion molecule (ICAM-1) blood serum levels.

From the pancreas and lungs removed of euthanized rats, tissue sections were prepared in a standard manner and stained with hematoxylin and eosin.

Macroscopic and microscopic changes were detected by points according to method [8]. With this aim the pancreatic and lungs tissue surface was temporarily divided into quadrants with an area of 0.01 cm^2, in each of which the parenchymal morphological changes were studied with inflammatory signs quantitative determination. The calculation was made in 10 quadrants of the studied organs removed from each rat [8].

The obtained results were statistically analysed using the Bonferroni parametric criterion. The minimum statistical significance threshold was set at $p<0.05$.

Results of the study and their discussion. Caerulein-induced AEP manifestation characterized by lipoperoxidation products significant accumulation as well as antioxidant enzymes activity suppression in pancreatic parenchyma. Both MDA and DC concentration reached maximal levels 24 hrs after the pathological condition induction and was characterized by these indexes increase by 2 and 2.6 times, correspondently (in all cases p<0.05; Table 1).

Table 1

The influence of octreotide on lipid peroxidation and antioxidant defense processes in rats with acute experimental pancreatitis

Experimental groups	The content of investigated substances in pancreatic tissue (M±m)			
	MDA, nmole/g	DC, μmole/g	SOD, U/g	GTP, U/g
12 hrs				
Control, n=6	3.11±0.21	0.41±0.04	1.82±0.17	2.67±0.19
AEP, n=7	5.61±0.43@	1.02±0.09@	0.94±0.08@	1.32±0.12@
AEP + NaCl, n=6	5.17±0.41	0.88±0.07	1.04±0.11	1.48±0.14
AEP + OT, n=6	4.87±0.37	0.91±0.08	0.98±0.11	1.29±0.12
24 hrs				
Control, n=6	3.09±0.23	0.44±0.04	1.67±0.16	2.58±0.21
AEP, n=6	6.33±0.47@	1.14±0.11@	0.89±0.08@	1.27±0.12@
AEP + NaCl, n=6	5.72±0.49	0.92±0.08	0.94±0.09	1.23±0.13
AEP+ OT, n=6	4.98±0.48	0.83±0.08	1.06±0.09	1.37±0.14
36 hrs				
Control, n=6	3.17±0.19	0.43±0.04	1.76±0.16	2.64±0.18
AEP, n=6	6.14±0.44@	1.08±0.09@	0.92±0.08@	1.36±0.12@
AEP + NaCl, n=6	4.81±0.46	0.69±0.07	1.08±0.11	1.58±0.14
AEP+ OT, n=6	3.24±0.28*#	0.47±0.04*#	1.57±0.14*#	2.29±0.18*#
48 hrs				
Control, n=6	3.14±0.23	0.46±0.04	1.84±0.17	2.54±0.19
AEP, n=6	4.67±0.42@	0.72±0.07@	1.16±0.09@	1.52±0.14@
AEP + NaCl, n=6	4.07±0.31	0.58±0.06	1.39±0.14	1.91±0.18
AEP+ OT, n=6	3.27±0.27*	0.44±0.04*	1.68±0.14*	2.42±0.19*
	The content of investigated substances in lung tissue (M±m)			
	MDA, nmole/g	DC, μmole/g	SOD, U/g	Catalase, μcat/g
12 hrs				
Control, n=6	1.16±0.09	0.76±0.06	1.84±0.16	4.09±0.23
AEP, n=7	2.34±0.16@	1.24±0.11@	1.09±0.09@	2.64±0.19@
AEP + NaCl, n=6	2.21±0.17	1.11±0.09	1.12±0.11	2.38±0.21
AEP + OT, n=6	2.09±0.18	1.02±0.08	0.91±0.11	2.77±0.24
24 hrs				
Control, n=6	1.24±0.11	0.73±0.06	1.76±0.17	4.16±0.21
AEP, n=6	2.96±0.21@	1.61±0.14@	0.83±0.07@	1.92±0.17@
AEP + NaCl, n=6	2.61±0.24	1.36±0.11	0.92±0.08	2.19±0.19
AEP+ OT, n=6	2.53±0.23	1.17±0.09	0.88±0.08	2.43±0.21
36 hrs				
Control, n=6	1.21±0.11	0.82±0.07	1.74±0.16	4.13±0.18
AEP, n=6	2.08±0.18@	1.17±0.11@	1.12±0.13@	2.83±0.22@
AEP + NaCl, n=6	1.79±0.16	0.91±0.08	1.39±0.13	3.11±0.28
AEP+ OT, n=6	1.68±0.16	0.74±0.06*	1.37±0.14	3.32±0.28
48 hrs				
Control, n=6	1.12±0.09	0.72±0.07	1.87±0.17	4.21±0.21
AEP, n=6	1.74±0.16@	0.96±0.08@	1.19±0.12@	3.11±0.27@
AEP + NaCl, n=6	1.64±0.16	0.83±0.07	1.44±0.13	3.52±0.32
AEP+ OT, n=6	1.27±0.12*	0.71±0.07*	1.82±0.16*	4.08±0.37*

Notes in all tables: @ – P<0.05 – statistical differences of the investigated parameters compared with the same in the control group; * – P<0.05 – statistical differences of the investigated parameters compared with the same in rats with AEP; # – P<0.05 – statistical differences of the investigated indexes compared with the same in rats with AEP injected with NaCl.

The pathological inflammatory process inside the pancreatic tissue was accompanied by SOD and GTP activity significant decrease which indexes 24 hrs of the trial reached 0.89±0.08 U/g and 1.27±0.12 U/g, respectively, which was 1.9 times and 2.0 times less compared with similar control indexes (in all cases $p<0.05$).

Octreotide injection 36 hrs from the beginning of the trial caused a significant MDA and DC concentrations decrease which were 1.9 and 2.3 times less if compared with corresponding indexes in pancreas of rats with AEP without treatment, and 32.6 % and 31.8 % less pertaining the same data in rats with AEP with NaCl injection (in all cases $p<0.05$).

SOD and GTP activities after OT administration increased in this time by 1.71 and 1.68 times, respectively, if compared with such indexes in rats with AEP without treatment, and also turned out to be 45.4 % and 44.9 % higher pertaining the same data in rats with AEP with NaCl injection (in all cases $p<0.05$).

Table 2

The influence of octreotide (OT) on morphometric indexes of investigated tissues in rats with acute experimental pancreatitis

Experimental groups	Pathomorphological changes in pancreatic tissue (M±m), points				
	Edema	Inflammation	Hemorrhage	Fat necrosis	Ascites, ml
12 hrs					
Control, n=6	-	-	-	-	-
AEP, n=7	3.21±0.28	1.16±0.13	2.61±0.22	2.67±0.24	4.22±0.39
AEP + NaCl, n=6	3.36±0.29	1.04±0.11	2.17±0.19	2.56±0.22	4.17±0.41
AEP + OT, n=6	3.16±0.27	1.07±0.12	2.12±0.19	2.64±0.23	4.26±0.41
24 hrs					
Control, n=6	-	-	-	-	-
AEP, n=6	2.87±0.27	1.32±0.13	2.48±0.21	2.73±0.26	6.88±0.62
AEP + NaCl, n=6	2.73±0.26	1.09±0.11	2.07±0.19	2.47±0.23	6.16±0.58
AEP+ OT, n=6	1.98±0.21*#	0.68±0.07*#	1.56±0.16*	2.68±0.24	4.18±0.39*
36 hrs					
Control, n=6	-	-	-	-	-
AEP, n=6	2.72±0.23	0.91±0.09	2.37±0.22	2.51±0.24	6.23±0.57
AEP + NaCl, n=6	2.21±0.21	0.82±0.08	1.82±0.17	2.32±0.21	5.08±0.49
AEP+ OT, n=6	1.51±0.14*#	0.48±0.05*#	1.37±0.14*	2.44±0.23	2.83±0.26*#
48 hrs					
Control, n=6	-	-	-	-	-
AEP, n=6	2.37±0.21	0.84±0.09	2.26±0.21	2.29±0.19	3.87±0.36
AEP + NaCl, n=6	1.83±0.19	0.61±0.08	1.63±0.17	1.86±0.17	2.69±0.26
AEP+ OT, n=6	1.38±0.13*#	0.27±0.03*#	1.07±0.09*#	1.63±0.16	1.72±0.16*#
	Pathomorphological changes in lung tissue (M±m), points				
	Edema	Inflammation	Alveolar volume	Alveolocyte membrane thickness	Neutrophilic infiltration
12 hrs					
Control, n=6	-	-	-	-	-
AEP, n=7	4.63±0.41	1.23±0.14	3.81±0.31	1.69±0.13	3.48±0.32
AEP + NaCl, n=6	4.17±0.39	0.92±0.09	3.79±0.32	1.58±0.14	2.86±0.28
AEP + OT, n=6	4.03±0.39	1.12±0.09	3.92±0.34	1.77±0.16	2.91±0.29
24 hrs					
Control, n=6	-	-	-	-	-
AEP, n=6	5.02±0.47	1.18±0.11	5.26±0.44	2.28±0.19	5.16±0.47
AEP + NaCl, n=6	4.81±0.46	0.79±0.08	4.81±0.39	2.04±0.18	4.64±0.41
AEP+ OT, n=6	3.69±0.36	0.87±0.09	4.39±0.39	1.96±0.17	3.79±0.34
36 hrs					
Control, n=6	-	-	-	-	-
AEP, n=6	4.16±0.38	0.86±0.08	4.09±0.37	1.93±0.18	4.26±0.39
AEP + NaCl, n=6	3.41±0.33	0.77±0.07	3.12±0.31	1.78±0.16	3.82±0.36
AEP+ OT, n=6	2.08±0.21*#	0.59±0.06	2.76±0.26*	1.39±0.14	2.96±0.28
48 hrs					
Control, n=6	-	-	-	-	-
AEP, n=6	3.58±0.33	0.76±0.07	3.66±0.33	1.72±0.16	3.37±0.32
AEP + NaCl, n=6	3.16±0.29	0.56±0.05	2.82±0.27	1.38±0.12	2.76±0.24
AEP+ OT, n=6	1.73±0.16*#	0.32±0.03*#	1.59±0.16*#	0.92±0.08*#	1.73±0.16*#

We recorded a similar OT-induced antioxidant activity changes in pancreatic tissue 48 hrs after the trial initiation. MDA and DC concentrations in the lung tissue also in rats with AEP significantly increased also with a simultaneous decrease in SOD and catalase activity the maximal expression of which lasted for 24 hrs ($p<0.05$).

Octreotide injection 48 hrs of the trial resulted in MDA and DC levels in the lung tissue equal to 1.27±0.12 nmol/g and 0.71±0.07 µmol/g which was 27 % and 26 % lower, respectively, when compared with such data in lungs of rats with AEP without treatment ($p<0.05$). A similar direction of OT corrective effect at this time of the experiment was registered in lungs tissue antioxidant enzymes activity restitution ($p<0.05$).

We observed pancreatic parenchyma edema and inflammation in the course of pancreatic gland pathomorphological examination, the presence of hemorrhages and fat necrosis as well as ascites. These specified pancreatic parenchyma damage pathomorphological criteria were maximally expressed during 36 hrs of the experiment (in all cases $p<0.05$; Table 2).

Pancreatic parenchyma both edema and inflammation indexes were equal to 1.98±0.21 and 0.68±0.07 points, respectively, after OT injection 24 hrs after the trial beginning which was 1.45 times and 1.94 times less pertaining the same indexes in rats with AEP without treatment and 27.5 % and 37.6 %, respectively, less if compared with such data in rats with AEP and NaCl administration (in all cases $p<0.05$).

The OT use at this time of the trial effectively eliminated hemorrhages in pancreatic tissue and reduced ascites ($p<0.05$). The OT impact on the investigated pancreatic tissue pathomorphological parameters had approximately the same expression also at 48 hrs of the trial ($p<0.05$).

Pneumocytes edema and inflammation, their size and cellular membrane thickening enlarge together with polymorphonuclear neutrophil infiltration significant increase were maximally expressed throughout the entire experiment (in all cases $p<0.05$). The OT administration was maximally effective only at the 48 hrs of the trials that was confirmed by all lung tissue inflammatory damage correlates expression significant decrease (in all cases $p<0.05$).

Caerulein-induced AEP manifestation was also accompanied by a significant increase in inducible NO-synthase activity (by 2.6 times), both TNFα and IL-1β content in blood serum (by 43 and 35 times, respectively) as well as ICAM-1 concentration by 1.84 times during the 24 hrs of the trial (in all cases $p<0.05$; Fig. 1).

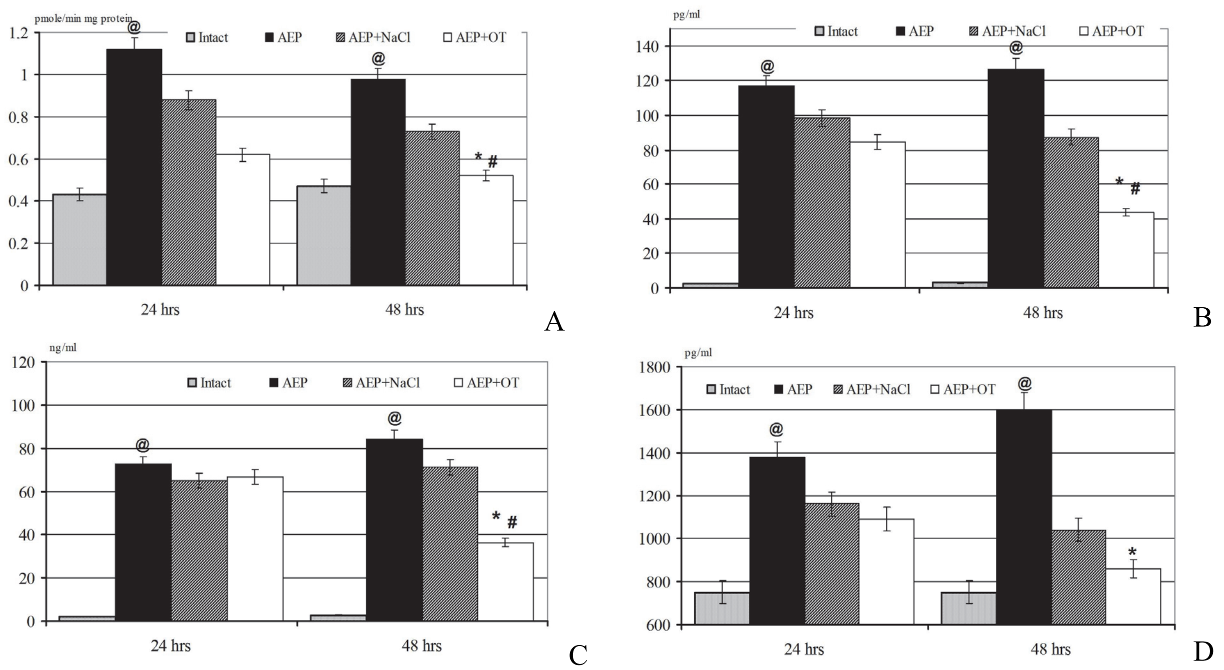

Fig 1. The influence of octreotide (OT) on blood serum biochemical correlates of inflammation in rats with acute experimental pancreatitis Notes – the same as in the tables.

The OT influence was significant only at 48 hrs of the experiment, when the activity of inducible NO-synthase in the blood serum decreased by 1.9 times compared to the same indicator in rats with untreated AEP ($p<0.05$). Both TNFα and IL-1β content was 2.9 times and 2.3 times less pertaining the same indexes in rats with AEP untreated and ICAM-1 concentration was on 86 % lower than in rats AEP without treatment (in all cases $p<0.05$). All absolute biochemical indexes obtained at the 48 hrs of the trial after OT injection were significantly less if compared with similar ones in rats with AEP with NaCl administration ($p<0.05$).

Thus, the data obtained indicate the expressed disturbances in functional system "lipid peroxidation – antioxidant defense" activity with its shift towards the lipoperoxidation products accumulation and the associated antioxidant enzymes activity inhibition in conditions of caerulein-induced AEP. Similar changes which are one of the universal cell death peroxide-induced mechanisms [12] we registered in pancreatic and lung tissues in these model condition of inflammatory genesis. All this was highlighted in conditions of pancreatic parenchyma acute caerulein-induced damage which, on the one hand, outlines the AEP pathogenetic mechanisms and, on the other hand, indicates the systemic nature of established damage processes in blood and in internal life-important organs.

Similar pathogenetic mechanisms of the body's' traumatic and hypoxic damage were studied in conditions of brain traumatic, ischemic stroke and acute traumatic pancreatitis. Therefore, analyzing both the obtained and issuing data one could guess the complex chains of pathobiochemical and pathophysiological reactions participating in pneumocytes and pancreatic cells irreversible necrotic changes development.

Interesting are the data about comparable with pancreatic shift in lipoperoxidation processes in the lungs. According to fundamental ideas one could suppose the pancreatic proteolytic enzymes release into blood after acinar cells necrosis contributes to cascade pathophysiological mechanisms "launch" which total activity resulted in lungs parenchyma failure by hyperactive enzymes, inflammatory and biologically active compounds together with peroxidative products activity.

This fact confirms the systemic nature of pancreatic gland inflammatory damage since the functional system "lipid peroxidation – antioxidant defense" pathological breakdown occurs in vital organs which importance is leading in body providing with oxygen and its protective, adaptive, compensatory and regulatory effects implementation.

Part of our results devoted to proving the inflammation "contribution" to pancreatic and lung tissue acute damage pathophysiological. This concerned the recognized pathogenetic importance of nitratergic and cytokine-dependent mechanisms. We also consider important the proved ICAM-1 content increase in lung damage in conditions of AEP. Briefly we want to state the following. The role of NO in mediating acute inflammatory reactions is known [13]. It is known also that NO synthesized via the activity of inducible NO synthase (iNOS) in conditions of acute inflammation contributes to vasodilation development, local damage of parenchyma of the organ that is the subject of inflammation and its subsequent ischemia [3]. Additionally, it's known that one of the characteristic effects of iNOS hyperactivation as a consequence of NO excessive production in vascular membrane muscle layers is vascular tone relaxation, a systemic arterial pressure decrease and bloodflow changes which are considered to be pathognomonic for acute pancreatitis and for lung damage in these conditions [3].

A significant increase in rats with AEP blood serum TNFα and IL-1β concentration indicates the proinflammatory cytokine system involvement in acute lung injury mediating in AEP. These cytokines levels increase in acute pancreatitis and acute lung injury due to pancreatitis also correlates with the severity of inflammation that corresponds to [9].

Trying to trace the chains of pathophysiological reactions in conditions of acute lung parenchyma injury we believe that the following sequence of pathobiochemical processes is most likely occur: the primary altering effect in conditions of caerulein-induced AEP is initiated by proinflammatory cytokines TNFα and IL-1β, one which effects is inflammation mediation via the iNOS the activation and NO formation. A similar sequence of events agreed by [12] emphasizing that iNOS activity also increases in response to release of gram-negative bacteria lipopolysaccharides and other biologically active compounds.

The increase the content of ICAM-1 – transmembrane protein that enables neutrophils to adhere to the endothelial surface – is logically integrated into the specified chain of pathophysiological mechanisms. It's reasonable to suppose that ICAM-1 has a pathogenetic significance in the mechanisms of lung damage in AEP, namely, it ensures the alveolar cells damage by activated polymorphonuclear neutrophils. Such a hypothesis is consistent with the findings of alveolocites fulminant necrosis in ICAM-1 knockout mice in conditions of AEP [15].

The investigated oxidative stress mechanism in conditions of caerulein-induced AEP, being one of the leading pathogenetic mechanisms, initiates cellular death in blood and internal organs parenchymal cells throughout the whole body.

A closed pathological circle is formed in these conditions in which one can clearly trace a cascade of interconnected pathological reactions initiated by altering pathological influence: leukocyte degranulation → biologically active compounds (proinflammatoiry cytokines) release → microcirculatory disorders → changes of blood rheological properties → the hypoxic and ischemic changes development → parenchymal internal organs cellular membranes damage → lipoperoxidation intensification and antioxidant defense suppression. Active radicals thus threaten cellular membranes activity to an even greater extent and contribute to the excessive influx of glutamate, calcium ions and other alterative components through defected membrane inside the cells which together represent the pancreatic gland, lungs and other vital organs pathogenetic mechanisms of apoptotic and necrotic cell death.

The final part of discussion is devoted to OT positive pneumoprotective effects in conditions of acute lung injury in AEP. Octreotide was shown to suppress approximately efficiently the intensity of lipoperoxidation and promotes the antioxidant enzymes activity increase in pancreatic and lung tissue. However, the profile of OT time-dependent efficacy in terms of peroxide changes in lungs correction lag behind its related intrapancreatic efficacy. The OT injection eliminated pathomorphological changes in pancreatic parenchyma with the exception of fat necrosis (at 36 hrs of the trial) and lung tissue (at 48 hrs of the trial). Finally, the iNOS activity, the content of pro-inflammatory cytokines and ICAM-1 in the blood serum of rats with AEP were significantly decreased as the result of OT impact. That is, the OT pneumoprotective action realization mechanisms included its antioxidant, antihypoxic and at least antiinflammatory effects which maximal efficacy occurred at 36-48 hrs of lung tissue inflammatory damage in AEP.

The mechanisms of OT pancreatoprotective effects already discussed in clinical conditions [7]. Both experimental and clinical data suppose to be important in terms of data obtained discussing and OT pneumoprotective effects mechanisms implementation identifying. It was proved that OT attenuated pancreatic gland failure [2] by inflammatory reaction decrease as well as hepatic ischemia/reperfusion mitigated [5] by pyroptosis expression suppression. Pyroptosis has recently known as a type of programmed cell death in which pancreatic cell damage is enhanced due to systemic inflammatory response acceleration with proinflammatory cytokines hasten expression [6].

Therefore, we consider the data obtained are the experimental evidence of inflammation and lipid peroxidation processes activation with antioxidant enzyme activity inhibition leading pathogenetic role in acute inflammatory pancreatic damage reaction that could also spread on lungs. We think that AEP complex pathogenetic treatment should include antioxidants and drugs with pneumoprotective activity. We believe that further pancreatic parenchyma cells acute inflammatory damage detailed mechanisms exploration will provide an opportunity to develop experimental scheme for AEP complex pathogenetically oriented correction and lung function restoration or their damage prevention.

Conclusions

1. The lipoperoxidation products accumulation and the antioxidant enzymes activity inhibition are recorded in pancreatic and lungs cells of rats with caerulein-induced AEP.

2. The caerulein-induced AEP manifestation is characterized by the expressed pancreatic and lungs cells pathomorphological changes predominantly of inflammatory origin.

3. Activation of the inducible NO-synthase, the increase of proinflammatory cytokines and intercellular adhesion molecules content is recorded in blood serum of rats with caerulein-induced AEP which highlights the pulmonary tissue damage predominant inflammatory pathophysiological origin.

4. The established pathophysiological mechanisms of lung damage in AEP reveal the systemic nature of the alteration which involve blood and the cells of vital organs.

5. The octreotide injection causes the of pneumoprotective effects development causes the pneumoprotective efficacy which mechanisms of implementation involve its antiinflammatory, antioxidant and antihypoxic effects. Pyroptosis inhibition is one of the probable mechanisms of octreotide pneumoprotective action realization.

6. The octreotide maximal pneumoprotective efficacy was recorded at 48 hrs of the trial which slightly lags behind the time of its pancreatoprotective effects (at 36 hrs of the trial).

7. The data obtained are the experimental evidence of octreotide clinical efficacy testing reasonability to prevent lung damage in acute inflammatory lesions of the pancreas.

Prospects for further research aimed at thorough investigation of pancreatic cells acute inflammatory damage to develop and check the efficiency of experimental scheme of lungs failure treatment and/or prevention in conditions of acute pancreatitis.

References

1. Vastyanov RS, Kirchev VV. Peroksydni mekhanizmy urazhen lehen pry eksperymentalnomu hostromu pankreatyti. Visnyk morskoyi medytsyny. 2024; 4(105): 143-151. doi: http://dx.doi.org/10.5281/zenodo. [in Ukrainian].
2. Borzsei R, Borbely E, Kantas B, Hudhud L, Horvath A, Szoke E. et al. The heptapeptide somatostatin analogue TT-232 exerts analgesic and anti-inflammatory actions via SST(4) receptor activation: in silico, in vitro and in vivo evidence in mice. Biochem Pharmacol. 2023; 209: 115419. doi: 10.1016/j.bcp.2023.115419.
3. Buchwalow I, Schnekenburger J, Samoilova V, Boecker W, Neumann J, Tiemann K. New Insight into the Role of Nitric Oxide Pathways in Pancreas. Acta Histochem Cytochem. 2018; 51(6): 167-172. doi: 10.1267/ahc.18028.
4. Chengjie L, Qi J. Maresin-1 Inhibits Oxidative Stress and Inflammation and Promotes Apoptosis in a Mouse Model of Caerulein-Induced Acute Pancreatitis. Med Sci Monit. 2019; 25: 8181-8189. doi: 10.12659/MSM.917380.
5. El-Sisi AEE, Sokar SS, Shebl AM, Mohamed, DZ, Abu-Risha SE. Octreotide and melatonin alleviate inflammasome-induced pyroptosis through inhibition of TLR4-NF-kappaB-NLRP3 pathway in hepatic ischemia/reperfusion injury. Toxicol. Appl. Pharmacol. 2021; 410: 115340. https://doi.org/10.1016/j.taap.2020.115340.
6. Gao L, Dong X, Gong W, Huang W, Xue J, Zhu Q. et al. Acinar cell NLRP3 inflammasome and gasdermin D (GSDMD) activation mediates pyroptosis and systemic inflammation in acute pancreatitis. Br J Pharmacol. 2021; 178: 3533–3552. https://doi.org/10.1111/bph.15499.
7. Huang L, Zhu H, Gu J. Octreotide and Continuous Hemofiltration versus Continuous Hemofiltration Alone in Severe Acute Pancreatitis Complicated with Acute Respiratory Distress Syndrome. J Coll Physicians Surg Pak. 2019; 29(8): 785-787. doi: 10.29271/jcpsp.2019.08.785.
8. Hughes CB, Gaber LW, El-Din ABM, Grewal HP, Kotb M, Mann L. et al. Inhibition of TNF-α improves survival in an experimental model of acute pancreatitis. Am Surg. 1996; 62(1): 8-13.
9. Kinaci E, Sevinc MM, Demir A, Erdogan E, Ahlatci FA, Idiz UO. Changes in cytokines and chemokines in an acute pancreatitis model. Ulus Travma Acil Cerrahi Derg. 2024; 30(4): 229-235. doi: 10.14744/tjtes.2024.18049.
10. Mederos MA, Reber HA, Girgis MD. Acute Pancreatitis: A Review. JAMA. 2021; 325(4): 382-390. doi: 10.1001/jama.2020.20317.
11. Mehta Y, Dixit SB, Zirpe K, Sud R, Gopal PB, Koul PA. et al. Therapeutic Approaches in Modulating the Inflammatory and Immunological Response in Patients With Sepsis, Acute Respiratory Distress Syndrome, and Pancreatitis: An Expert Opinion Review. Cureus. 2021; 13(9): e18393. doi: 10.7759/cureus.18393.
12. Muszynski JA, Thakkar R, Hall MW. Inflammation and innate immune function in critical illness. Curr Opin. Pediatr. 2016; 28: 267-273. doi: 10.1097/MOP.0000000000000352.
13. Sinningen K, Emons B, Böhme P, Juckel G, Hanusch B, Beckmann B. et al. l-Arginine/nitric oxide pathway and oxidative stress in adults with ADHD: Effects of methylphenidate treatment. Nitric Oxide. 2023; 138-139: 64-69. doi: 10.1016/j.niox.2023.06.006.
14. Szatmary P, Grammatikopoulos T, Cai W, Huang W, Mukherjee R, Halloran C. et al. Acute Pancreatitis: Diagnosis and Treatment. Drugs. 20228 2(12): 1251-1276. doi: 10.1007/s40265-022-01766-4.
15. Xiao Z, Wilson C, Robertson HL, Roberts DJ, Ball CG, Jenne CN. et al. Inflammatory mediators in intra-abdominal sepsis or injury – a scoping review. Crit Care. 2015; 19: 373. doi: 10.1186/s13054-015-1093-4.

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