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IMPACT OF INFUSION THERAPY ON STRUCTURAL CHANGES IN RAT ADENOHYPOPHYSIS IN EXPERIMENTAL DERMAL BURN INJURY

Summary. *The paper presents data related to the autophagy and crinophagy in rat adenohipophysis in treatment of burn injury by the infusion of lactoprotein with sorbitol and HAES-LX-5%. It has been established that intravenous infusion of lactoprotein with sorbitol in rat experimental burn disease leads to structural transformations of histohematic barrier when interaction of vascular wall cells and endocrine cells enables the formation of "collateralized membrane complex" in the adenohipophysis. Administration of lactoprotein with sorbitol and HAES-LX-5% inhibits structural manifestations of cell death and ensures the life saving of adenohipophysis endocrine cells by involvement of mechanisms for autophagy and crinophagy. Crinophagy of endocrine cells in the adenohipophysis is adaptive in nature; it ensures elimination and disposal of excess hormones, distorted as a result of catabolic reaction, specific for burn disease. Autophagy is activated in case of urgent (emergency) need to extrude the damaged organelles together with adjacent areas of cytoplasm.*

Key words: burn injury, infusion therapy, adenohipophysis, light and electron microscopy.

Introduction

Admittedly, burn pathology is not limited to superficial injury to tissues; major (if the superficial burn surface exceeds 10%) and deep burns cause versatile structural and functional impairment of internal body organs and systems [Keck et al., 2009]. It is precisely the infusive therapy with polyfunctioning agents that is a mandatory compound of comprehensive treatment of burn disease [Kozinets et al., 2005].

At the same time there is a well-founded opinion [Derkach, 2008; Cherkasov, 2011; 2015; Kovalchuk et al., 2014], that the lack of objective scientifically substantiated information is not the hindrance to reasonable implementation of the novel solutions into clinical practice. In this regard, the issue of "whether novel infusion agents contribute to discovery of advanced therapeutic opportunities"

remains relevant [Georgeyanu, Korsunov, 2008].

Purpose. The research was aimed at clearing up the peculiarities of morphological effects of adenohipophysis response to infusion with composite hyperosmolar solutions (disintoxicative, rheological and antishock effect) and infusion with sodium chloride isotonic solution in dermal burn injury.

Materials and Methods

90 Wistar male rats, weighted 155-160 g, involved into experimental study of morphological changes in adenohipophysis in burn injury (in 1, 3, 7, 14, 21, 30 days), were infused with 0,9% NaCl solution in combination with HAES-LX-5% (the novel domestic blood substitute) and lactoprotein with sorbitol (the brand name is "Lactoprotein-C®") colloidal hyperosmolar agents.

Animal housing and experiments on them have been carried out in compliance with the "General Ethic Rules for Conducting Experiments on Animals", approved by the First National Bioethics Congress (Kyiv, 2001), and the requirements of international principles of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (Strasbourg, 1985), as well as the principles of "Good laboratory practice for safety tests on chemicals (GLP)".

The animals were assigned into 7 groups: Group I - intact animals; Group II, III, IV - rats without burn injury, individually infused with 10 ml/kg of 0,9% NaCl solution, HAES-LX-5% and Lactoprotein-C®, respectively; Group V, VI, VII - burned animals, administered with the investigated agents according to the regimen and dose, similar to animals of Group II, III, IV.

The burn (after relevant premedication) was induced by placing of four copperplates, pre-soaked in water at 100 °C for 6 min, to the lateral surfaces of the animals' body (two plates per each side). The total superficial burn surface of rats with specified weight accounted for 21-23% in 10 sec exposure that was sufficient for initiation of the second-degree burn, i.e., dermal superficial partial-thickness burn (former III-A degree) and the development of shock of moderate severity.

The investigated solutions were administered intravenously during 5-6 min in a dose of 10 ml/kg body weight. The infusion was conducted in the lower hollow vein with its catheterization through the femoral vein, made in aseptic conditions. Catheter, inserted into the femoral vein, was sewed subcutaneously. Its lumen was filled with heparin titrating solution (0,1 ml heparin per 10 ml 0,9% NaCl solution) along its entire length after each administration of agents. The first administration of solutions was made in 1 hour after simulation of pathological state, and the follow-up infusions were performed daily during 7 days.

Material sampling was made under anesthesia. After animals' decapitation the autopsy of thoracic cavity was made and small pieces of thymus were cut with razor blade. Material for morphological analysis was prepared in compliance with the standard procedure.

Ultrathin sections were prepared in the "LKB" ultramicrotome, analyzed and photographed on PEM-125K electron microscope. Semithin sections were stained with toluidine blue, analyzed and photographed, using Olympus BX51 light microscope.

The experiment was carried out on the basis of the Research Center at N.I. Pirogov Vinnitsa National Medical University. Electron microscope analysis was made at the Department of Electron Microscopy (supervisor, Professor L.O. Stechenko), Institute of Pathology Problems at Bogomolets National Medical University.

Results and Discussion

The additional study (Table 1) of the impact of infusion of 0,9% NaCl solution, lactoprotein with sorbitol and HAES-

Table 1. The effect of pharmacotherapy with 0,9% NaCl solution, lactoprotein with sorbitol and HAES-LX-5% on lethality rate of rats with dermal burn injury.

| Conditions of the experiment | Lethality of animals | | | | | |
|---|----------------------------------|----------------|-------------|-------------|-------------|-------------|
| | Time period of observation (day) | | | | | |
| | 1 | 2-3 | 4-7 | 8-14 | 15-21 | 22-30 |
| Burn + 0,9 % NaCl solution (n=200) | n=10 (5 %) | n=21 (10,5- %) | n=22 (11%) | n=17 (8,5) | n=11 (5,5%) | n=6 (3 %) |
| Burn + HAES-LX-5 % (n=120) | n=2 (1,7 %) | n=4 (3,3%)* | n=5 (4,2%)* | n=4 (3,3%)# | n=2 (1,7 %) | n=1 (0,8 %) |
| Burn + lactoprotein with sorbitol (n=120) | n=1 (0,8 %) | n=4 (3,3%)* | n=3 (2,5%)* | n=3 (2,5%)* | n=1 (0,8%) | n=3 (1,7 %) |

Notes: * - reliable difference regarding the control (burn + 0,9 % NaCl); # - tendency of difference regarding the control (burn + 0,9 % NaCl).

LX-5% on the rates of lethality of rats with dermal burn injury showed the undeniable benefits of the applied colloidal hyperosmolar agents.

The group of animals with dermal burn injury, administered with 0,9% NaCl solution, showed progressing increase of the lethality rate from 5% after day 1 to 11% in the interval from day 4 to day 7 with follow-up lowering of the rate value up to 3% in the interval from day 22 to day 30 after skin burn. The total lethality rate in the group of male rats, administered with 0,9% NaCl solution after skin burn, accounted for 43,5%. The specific therapeutic course treatment of burned rats with HAES-LX-5% solution, similar to lactoprotein with sorbitol significantly prevented death of animals throughout the observation.

The benefits of the applied colloidal hyperosmolar solutions can be explained by the fact that the isotonic solution of sodium chloride is similar to blood plasma for osmolarity and content of ions of sodium only, but chlorine ions content is much higher [Shlapak et al., 2008]. However, lactoprotein with sorbitol and HAES-LX-5% contain the components of polyfunctional effect, which along with the hemodynamic action, provide the correction of water-electrolytic, protein, energy imbalances, adjust the acid-base blood status, force diuresis, and attenuate manifestations of intoxication.

Lactoprotein with sorbitol is an infusion colloidal hyperosmolar agent [Kondratskiy et al., 2004] that contains albumin (5%), sorbitol (6%), sodium lactate (21.1%), as well as electrolytes in balanced amount. Theoretical osmolarity of the agent is 1020 mOsm/l. HAES-LX-5% is a composite colloidal hyperosmolar infusion agent which contains hydroxyethylated starch with MM 130000, xylitol quinquatomic alcohol, sodium lactate alkalizing agent, salts of sodium, potassium, calcium and magnesium chlorides as a colloid base. Osmolarity of the agent is 890mOsm/l, which is three times higher than the osmolarity of sodium chloride isotonic solution and osmolality of blood plasma.

The study showed the significant differences in the effects

of sodium chloride isotonic solution and composite colloidal hyperosmolar solutions on adenohypophysis structure of burned rats. Thus, after day 1, 3, 7 and 14 of the experiment (time periods when the increase and stabilization of the value of lethality rate was recorded) in adenohypophysis of rats with dermal burn injury, administered with 0,9% NaCl solution, the most specific common manifestation of pathomorphological changes was the alteration of functionally different cells of organs and vascular walls of hemomicrocirculatory stream, concomitant with mosaic, but sometimes pronounced (especially after day 1) intercellular and paravasal edemas and hemorrhages.

Partial and total necrosis of endotheliocytes is noted in the wall of some blood capillaries and veins; thinning and local destruction of basal membrane occurs; paravasal hemorrhages are originated.

Changes in configuration of interendothelial joints lead to occurrence of enlarged interendothelial openings or transendothelial canals in the area of simple-shaped and short-length interendothelial joints, presented in the form of end-to-end transmural defects in the areas of corresponding loci of basal membrane destruction. The described transmural defects coupled with the adjacent and dilated (as a result of the edema development) intercellular spaces of the investigated organs are the sites of plasma and blood cells "leakage" and intraorganic "penetration", leading to edema and haemorrhages progression.

In rats with burn injury, administered with hyperosmolar solutions according to the regimen of the experiment, no significant damage to vascular walls and haemorrhages was detected in the adenohypophysis, as well as, correspondingly, no structural signs of paravasal and intercellular edema were found. This indicates about the angioprotective properties of the applied composite hyperosmolar solutions, providing with rather specific membranoflexible effect if used in combination with lactoprotein with sorbitol.

Our previous studies [Gunas et al., 2014; Kovalchuk et al., 2014] demonstrate, that intravenous infusion of lactoprotein with sorbitol and HAES-LX-5% inhibits the process of endogenous intoxication, and, therefore, ensures prolongation of phase of relative resistance, as well as activation of mechanisms of compensatory-adaptive and regenerative processes in the adenohypophysis in conditions of investigated experimental burn injury. Infusion of lactoprotein with sorbitol leads to structural transformations of the histohematogenous barrier, when the interaction of vascular wall's cells with endocrine cells resulted in formation of the "perivasal membrane complex with lateral branches" or simply "collateralized membrane complex" in adenohypophysis parenchyma of rats from experimental Group IV. This collateralized membrane complex is formed in the areas of "leakages" and "penetrations", containing electron-dense homogenous contents (transformed components of lactoprotein with sorbitol?) of the lumen of adenohypophysis blood capillaries (Fig. 1). Formation of

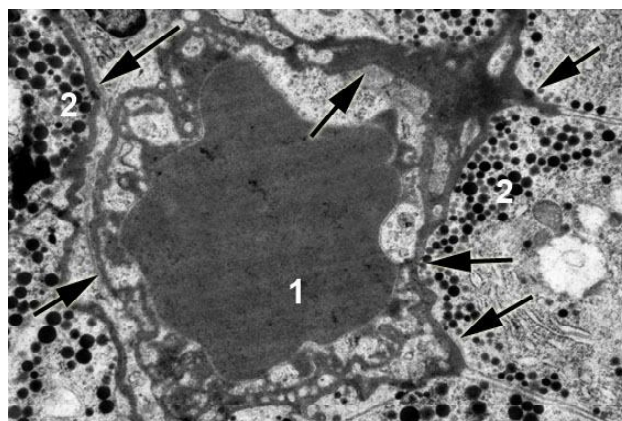


Fig. 1. Formation of collateralized membrane complex (marked with arrows) in the areas of "leakages" and "penetrations" in rat adenohypophysis following the 7 days after experimental burn injury in administration of lactoprotein with sorbitol. 1 - electron-dense contents of blood capillary lumen; 2 - fusion of secretory granules with lysosomes and destruction of membrane of transformed secretory granules in somatotrophocyte cytoplasm. Original magnification x 10000.

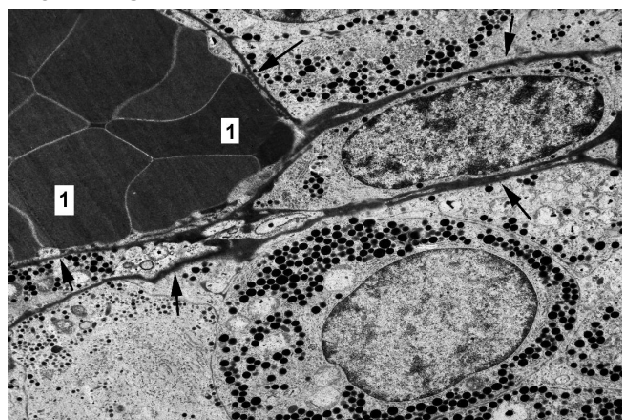


Fig. 2. Membrane structures (marked with arrows), incorporated into collateralized membrane complex, lead to persistent changes in cytoarchitecture of rat adenohypophysis following the 21 days of burn disease development in administration of lactoprotein with sorbitol. 1 - red blood cells in the lumen of postcapillary venule. Original magnification x 8000.

membrane structures causes stable modifications of adenohypophysis cytoarchitecture, observed even at the late stages of the experiment (Fig. 2).

It has been established that part of the adenohypophysis endocrine cells at the stages of the burn injury development degrade due to apoptosis and necrosis. It has been also ascertained that administration of lactoprotein with sorbitol and HAES-LX-5% inhibits structural manifestations of cell death and contributes to saving life of adenohypophysis cells due to involvement of mechanisms for autophagy and crinophagy.

The autophagy initiation is proved by evident surrounding and sequestration of cellular organelles and loci of compaction of microgranular cytoplasmic matrix by the isolation membrane (phagophor). The most typical and

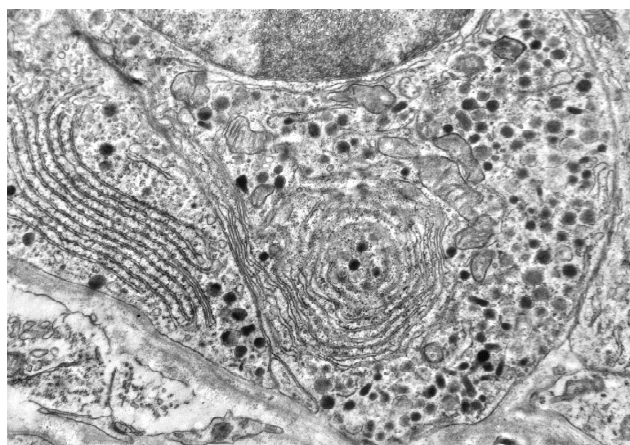


Fig. 3. Concentric aggregation of canaliculi of granular endoplasmic reticulum (as the initial stage of autophagosome formation) in the cytoplasm of corticotrophocyte of rat adenohypophysis following the 3 days after experimental burn injury in administration of lactoprotein with sorbitol. Original magnification x 15000.

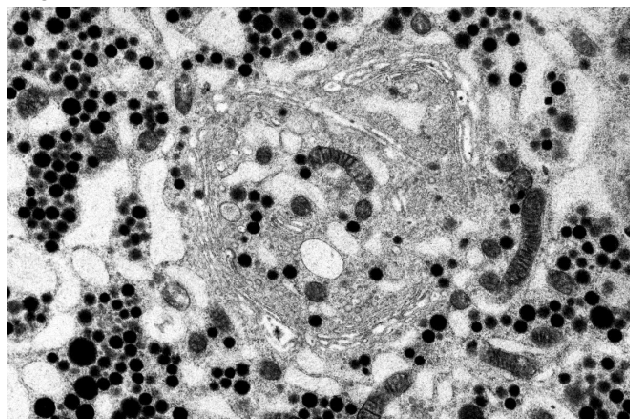


Fig. 4. Maturation of autophagosome in the cytoplasm of somatotrophocyte of rat adenohypophysis following the 7 days after experimental burn injury in administration of lactoprotein with sorbitol. Original magnification x 16000.

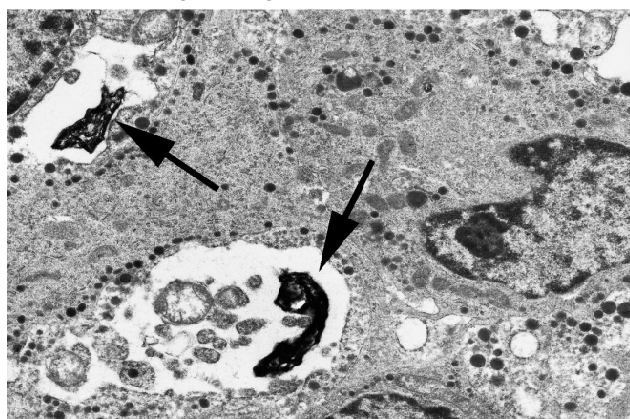


Fig. 5. Degradation of contents of autophagolysosomes (marked with arrows) in the cytoplasm of corticotrophocyte of rat adenohypophysis following the 7 days after experimental burn injury in administration of lactoprotein with sorbitol. Original magnification x 14 000.

common option for the phagophors origination is (Fig. 3, Fig. 4) concentric aggregation of canaliculi of granular endoplasmic reticulum around the "nucleus" (secretory granules, aggregated proteins, damaged mitochondria and canaliculi of endoplasmic reticulum). Concentric circles are appeared when the ends of canaliculi of endoplasmic reticulum are joined together. As a result, a closed autophagosome is formed.

The resulting data showed that autophagosomes in the cells of adenohypophysis are subjected to gradual process of the development, including their fusion with lysosomes and formation of autophagolysosomes. The latter provides with isolated contact of sequestered cytoplasmic contents with lysosomal components, their fusion and degradation. The subsequent destruction of the inner membranes, autophagosome contents (Fig. 5) and, finally, its transformation into autophagic vacuole (Fig. 6) with electron-clear contents occur. Autophagic vacuoles persist within the cytoplasm of adenohypophysis endocrine cells for a long time, and then after fusion with cytolemma, extrude its contents.

Sometimes the sequence of events in autophagy somehow changes and at different stages of maturity autophagosomes are grouped together, forming the complexes of structures that initially were non-surrounded by phagophor (Fig. 7).

The common feature of response of all adenohypophysis endocrine cells (regardless of the degree of structural manifestations of secretory activity) in burned rats, administered with lactoprotein with sorbitol and HAES-LX-5% is crinophagy. In 1966 R.E. Smith and M.G. Farquhar were the first who found this phenomenon of the specific interaction of lysosomes with secretory granules [Smith, Farquhar, 1966].

In crinophagy (in contrast to autophagy) no prior isolation of areas of cytoplasm of adenohypophysis endocrine cells with secretory granules by membrane elements occurs; however, digestion of contents of lysosomes by secretory granules occurs in conditions of actual fusion of these organelles (Fig. 1, Fig. 6, Fig. 8). Direct fusion of secretory granules with lysosomes at all stages of their maturation (from the early endosomes in the form of small membrane vesicles with electron-clear contents to late endosomes and initial lysosomes in the form of small membrane vesicles with electron-dense contents) leads to degradation or modification of secretory material. After fusion with cytolemma the transformed secretory granules extrude its contents (exocytosis) or destruction of membrane of transformed secretory granule occurs in cytoplasm. In the latter case products of hydrolytic transformation of contents of secretory granules diffuse through cytolemma into pericapillary space and release into bloodstream through the fenestres of endothelium of blood capillaries.

Coming back to discussion of mechanisms of origination of electron-dense collateralized membrane complex in adenohypophysis of rats from experimental group IV, it

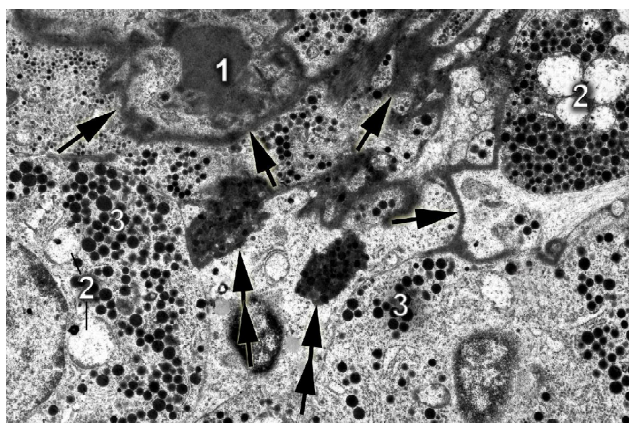


Fig. 6. Simultaneous combination of autophagy and crinophagy in the cytoplasm of somatotrophocytes of rat adenohypophysis following the 7 days after experimental burn injury in administration of lactoprotein with sorbitol. Collateralized membrane complex is marked with single arrows; autophagolysosomes in secretory granules at different stages of transformation are marked with double arrows. 1 - electron-dense contents of blood capillary lumen; 2 - autophagic vacuoles; 3 - fusion of secretory granules with lysosomes (crinophagy). Original magnification x 6000.

should be noted that the role of phagocytic and secretory activity of endocrine cells, expressed by crinophagy and autophagy, might be structure-forming. In this case transformed proteins and amino acids that are products of complete or incomplete digestion of adenohypophysis peptide hormones in secretory granules with incorporated contents of lysosomes and autophagolysosomes move into intercellular spaces. Here they join the "leakages" and "penetrations" loci of lactoprotein with sorbitol components, as well as their derivatives, formed as a result of interaction with endotoxins and products of liver detoxification activity. We hypothesize that it is rather complicated scenario for events that leads to initiation of unique structure formation, i.e., collateralized membrane complex in adenohypophysis.

The resulting data proved that crinophagy in adenohypophysis endocrine cells is of adaptive nature; it ensures elimination and disposal of excess hormones, distorted as a result of catabolic reaction, specific to burn disease [Levine, Kroemer, 2008]. Autophagy, being the energy consuming process [Cherkasov, 2011; 2015; Levine, Kroemer, 2008; Choi, Ryter, Levine, 2013; Werman et al., 2014], is activated in case of urgent (emergency) need to dispose the damaged organelles together with adjacent areas of cytoplasm. In all cases, crinophagy and autophagy is accompanied by expressive lysosomal reaction. Sometimes the contents of lysosomes are disposed into cytosol, initiating cell self-destruction, i.e., autolysis. We hypothesize that the route of cell death of adenohypophysis endocrine cells in burn disease is determined by the degree and controllability of lysosomal reaction: if the massive damage of lysosomes or autophagolysosomes leads to necrosis, then the controlled disposal of the lysosomal enzymes into cytosol can cause the onset of apoptosis.

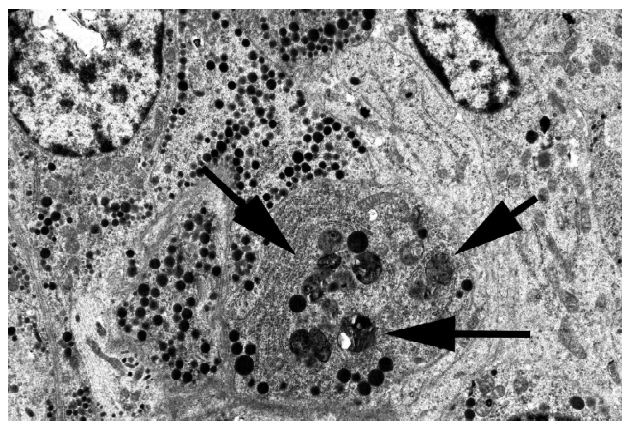


Fig. 7. Aggregation of autophagosomes at different stages of maturation in cytoplasm of somatotrophocyte of rat adenohypophysis following the 7 days after experimental burn injury in administration of HAES-LX-5%. Original magnification x 16000.

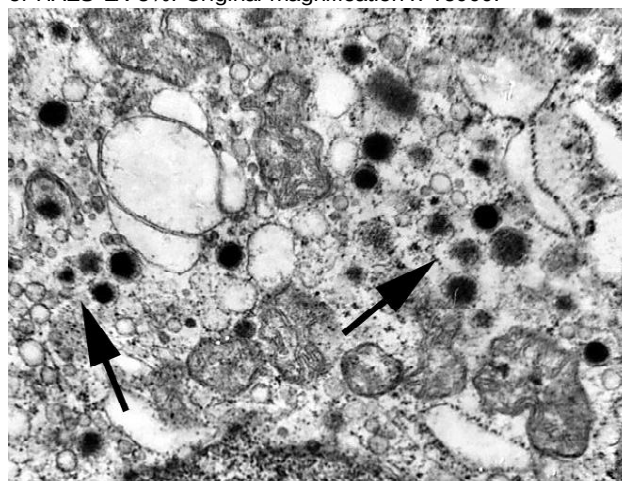


Fig. 8. Crinophagy in the form of origination of fusion areas (marked with arrows) of small membrane vesicles with electron-clear and electron-dense contents (lysosomes at different stages of maturation) with secretory granules (leading to destruction of the latter) in the cytoplasm of corticotrophocyte of rat adenohypophysis following the 7 days after experimental burn injury in administration of HAES-LX-5% Original magnification x 20000.

Conclusions

1. Study of the impact of lactoprotein with sorbitol on adenohypophysis structure in dermal burn injury has revealed its specific effect, enabling the advanced therapeutic possibilities to use the agent as angioprotector with membranoflexible properties. Angioprotective and membranoflexible properties of lactoprotein with sorbitol are ultrastructurally reflected by the ability of its transformed components, interacted with vascular wall cells and endocrine cells to initiate the formation of "collateralized membrane complex" in rat adenohypophysis parenchyma.

2. Lactoprotein with sorbitol and HAES-LX-5% demonstrate its cytoprotective properties, ensuring prolongation of relative resistance phase, as well as initiation of mechanisms for compensatory adaptive and regenerative processes in adenohypophysis in the experimental burn

injury. Administration of lactoprotein with sorbitol and HAES-LX-5% contribute to saving life of adenohipophysis cells due to involvement of mechanisms for autophagy and crinophagy. Crinophagy in adenohipophysis endocrine cells is of adaptive nature; it ensures elimination and disposal of excess hormones, distorted as a result of catabolic reaction, specific to burn disease. Autophagy is activated in case of urgent (emergency) need to dispose the damaged organelles together with adjacent areas of cytoplasm.

3. Infusion therapy with lactoprotein with sorbitol and HAES-LX-5% are highly effective (as compared to infusion with NaCl isotonic solution) treatment of the consequences of extended (21-23% of the surface) skin burns. The resulting data showed that infusion with colloid-hyperosmolar solutions is quite aggressive method of intervention that involves the potential occurrence of

unexpected side effects (such as the change in cytoarchitectonics in conditions of infusion of lactoprotein with sorbitol into adenohipophysis in skin burn). The follow up scientific research and development of the novel infusion solutions that will be able to provide maximum therapeutic effect against the minimal complications is crucial. The analysis of differences in morphofunctional manifestations that were revealed in administration of conventional infusion solutions during the treatment of specific pathological conditions in a wide range of diseases remains relevant to date.

The perspectives of further research are encompassed the cytophotometric analysis of the cell cycle and apoptosis indicators in animal adenohipophysis in experimental dermal burn injuries in conditions of infusion of lactoprotein with sorbitol and HAES-LX-5% solutions.

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ВПЛИВ ІНФУЗІЙНОЇ ТЕРАПІЇ НА СТРУКТУРНІ ЗМІНИ АДЕНОГІПОФІЗА ЩУРІВ ПРИ ЕКСПЕРИМЕНТАЛЬНІЙ ОПІКОВІЙ ТРАВМІ ШКІРИ

Резюме. У статті наведені результати дослідження автофагії і кринофагії в аденгогіпофізі щурів за умов лікування опікової хвороби інфузією лактопротеїну з сорбітолом та HAES-LX-5%. Встановлено, що внутрішньовенна інфузія лактопротеїну з сорбітолом за умов експериментальної опікової хвороби у щурів призводить до структурних трансформацій гістогематичного бар'єру, коли співдружність клітин судинної стінки та ендокринних клітин забезпечує формування "колатералізованого мембранного комплексу" в аденгогіпофізі. Введення лактопротеїну з сорбітолом та HAES-LX-5% гальмує структурні прояви клітинної загибелі та сприяє збереженню життя ендокринних клітин аденгогіпофіза за рахунок залучення механізмів автофагії та кринофагії. Кринофагія в ендокринних клітинах аденгогіпофіза носить адаптивний характер; вона забезпечує знищення і виділення надлишкової кількості гормонів, що є спотвореними у результаті характерної для опікової хвороби катаболічної реакції. Автофагія спрацьовує у разі нагальної (аварійної) потреби видалення ушкоджених органел разом з прилеглими ділянками цитоплазми.

Ключові слова: опікова травма, інфузійна терапія, аденгогіпофіз, світлова та електронна мікроскопія.

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ВЛИЯНИЕ ИНФУЗИОННОЙ ТЕРАПИИ НА СТРУКТУРНЫЕ ИЗМЕНЕНИЯ АДЕНОГИПОФИЗА КРЫС ПРИ ЭКСПЕРИМЕНТАЛЬНОЙ ОЖГОВОЙ ТРАВМЕ КОЖИ

Резюме. В статье представлены результаты исследования автофагии и кринофагии в аденогипофизе крыс в условиях лечения ожоговой болезни инфузией лактопротеина с сорбитолом и HAES-LX-5%. Установлено, что инфузия лактопротеина с сорбитолом в условиях экспериментальной ожоговой болезни у крыс приводит к структурным трансформациям гистогематического барьера, когда содружественная деятельность клеток сосудистой стенки и эндокринных клеток обеспечивает формирование "коллатерализованного мембранного комплекса" в аденогипофизе. Введение лактопротеина с сорбитолом и HAES-LX-5% тормозит структурные проявления клеточной гибели и способствует сохранению жизни эндокринных клеток аденогипофиза за счет привлечения механизмов автофагии и кринофагии. Кринофагия в эндокринных клетках аденогипофиза носит адаптивный характер; она обеспечивает уничтожение и выделение избыточного количества гормонов, является искаженными в результате характерной для ожоговой болезни катаболической реакции. Автофагия срабатывает в случае срочной (аварийной) потребности удаления поврежденных органелл вместе с прилегающими участками цитоплазмы.

Ключевые слова: ожоговая травма, инфузионная терапия, аденогипофиз, световая и электронная микроскопия.

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