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MORPHOMETRIC AND HISTOCHEMICAL CHARACTERISTICS OF THE ESOPHAGEAL EPITHELIUM AFTER ADMINISTRATION OF MORPHOGEN AND CYTOSTATIC DRUG

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Abstract. ***Introduction.*** Esophagitis of various etiologies, metaplasia (Barrett's disease) and cancer are a serious problem at the current stage of medical development. Understanding the regulation of esophageal epithelial proliferation and differentiation is crucial for developing effective therapeutic strategies. ***The aim of the study*** was to conduct a comparative analysis of the effects of the peptide morphogen hydra and the cytostatic drug cyclophosphamide on the morphometric and histochemical parameters of the esophageal epithelium in mice, with special attention to changes in tissue organization characterized as heteromorphism. For the first time, a comprehensive approach combining morphometric, histochemical, and immunohistochemical methods is presented to assess the effect of these drugs on epithelial cell proliferation and metabolism. ***Materials and methods.*** 45 white mongrel mice were used in the experiment. Groups of animals were injected intraperitoneally with the peptide morphogen hydra (PMG) (100 mcg/kg) or cyclophosphamide (CF) (400 mg/kg) for 5 days, the control group received saline solution. Histological analysis, morphometry, histochemistry (NADH-diaphorase and succinate dehydrogenase activity), and immunohistochemistry (detection of nuclear antigen of proliferating PCNA cells) were performed 24 hours after the last injection. ***The results*** showed that the peptide morphogen of hydra induces epithelial hyperplasia, mainly due to the spiny layer, and increases the activity of NADH-diaphorase and succinate dehydrogenase, as well as the proliferative index. Cyclophosphamide causes hyperkeratosis, impaired differentiation, and decreased enzyme activity, with a paradoxical initial increase and then decrease in proliferative activity. ***Conclusions.*** The peptide morphogen of hydra and cyclophosphamide cause opposite changes in the epithelium of the esophagus, enhancing its heteromorphism. The data obtained are important for understanding the pathogenesis of chemotherapy complications and developing new strategies for the treatment of esophageal diseases.

Keywords: esophageal epithelium, heteromorphy, cyclophosphamide, morphogen

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ВЛИЯНИЕ ПЕПТИДОГО МОРФОГЕНА ГИДРЫ И ЦИКЛОФОСФАНА НА МОРФОМЕТРИЧЕСКИЕ И ГИСТОХИМИЧЕСКИЕ ПАРАМЕТРЫ ЭПИТЕЛИЯ ПИЩЕВОДА МЫШЕЙ

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Резюме. ***Введение.*** Эзофагиты различной этиологии, метаплазия (болезнь Барретта) и рак представляют серьезную проблему на современном этапе развития медицины. Понимание регуляции пролиферации и дифференцировки эпителия пищевода критически важно для разработки эффективных терапевтических стратегий. ***Цель исследования*** — провести сравнительный анализ воздействия пептидного морфогена гидры и цитостатического препарата циклофосфана на морфометрические и гистохимические параметры эпителия пищевода у мышей, с особым вниманием к изменениям тканевой организации, характеризующимся как гетероморфия. Впервые представлен комплексный подход, объединяющий морфометрические, гистохимические и иммуногистохимические методы для оценки влияния этих препаратов на пролиферацию и метаболизм эпителиальных клеток. ***Материалы и методы.*** В эксперименте использовали 45 белых беспородных мышей. Группам животных вводили внутрибрюшинно пептидный морфоген гидры (ПМГ) (100 мкг/кг) или циклофосфана (ЦФ) (400 мг/кг) в течение 5 дней, контрольная группа, получала физиологический раствор. Гистологический анализ, морфометрия, гистохимия (активность НАДН-диафоразы и сукцинатдегидрогеназы) и иммуногистохимия (выявление ядерного антигена пролиферирующих клеток PCNA) проводились через 24 часа после последней инъекции. ***Результаты*** показали, что пептидный морфоген гидры индуцирует гиперплазию эпителия, преимущественно за счет шиповатого слоя, и повышает активность НАДН-диафоразы и сукцинатдегидрогеназы, а также пролиферативный индекс. Циклофосфан вызывает гиперкератоз, нарушение дифференцировки и снижение активности ферментов с парадоксальным начальным увеличением, а затем снижением пролиферативной активности. ***Выводы.*** Пептидный морфоген гидры и циклофосфан вызывают противоположные изменения в эпителии пищевода, усиливая его гетероморфию. Полученные данные важны для понимания патогенеза осложнений химиотерапии и разработки новых стратегий лечения заболеваний пищевода.

Ключевые слова: эпителий пищевода, гетероморфия, циклофосфан, пептидный морфоген гидры

INTRODUCTION

Diseases of the esophagus, including esophagitis of various etiologies, metaplasia (Barrett's disease) and cancer, represent a serious medical problem [7, 9, 14]. Understanding the regulation of esophageal epithelial proliferation and differentiation is critical for the development of effective therapeutic strategies [10, 11, 15]. In this study, we compared the influence of two agents with opposite mechanisms of action on esophageal epithelium: peptide morphogen hydra (PMG), known for its regenerative properties, and cyclophosphamide (CPh), a cytostatic drug widely used in oncology. The study hypothesis was that these agents would induce opposite changes in epithelial morphometry and histochemistry.

AIM

The aim of the study is to conduct a comparative experimental investigation of changes in the histological structure of the esophageal mucosal epithelium, its proliferative and metabolic activity under the influence of a cytostatic agent and a morphogen, taking into account the heteromorphism of this tissue

MATERIALS AND METHODS

The experiment was conducted on 45 adult outbred white male mice (23–25 g), randomly divided into three groups of 15 animals each: control (intraperitoneal administration of physiological NaCl solution), PMG group (intraperitoneal administration of PMG at a dose of 100 μg/kg body weight), CPh group (intraperitoneal administration of CPh, LENS-Pharm, Russia, 400 mg/kg body weight). Daily intraperitoneal administration of the drugs was carried out for 5 days. 24 hours after the last injection, the animals were euthanized [2]. Esophageal samples were fixed in Carnoy's fluid, histological sections were prepared, and hematoxylin and eosin staining was performed. Morphometric analysis (thickness of the epithelial layer and its parts) was performed using an ocular micrometer (×280). Proliferative activity was assessed by counting mitoses in the basal layer (≥3000 cells per animal, ×900). NADH diaphorase (NADH-d) and succinate dehydrogenase (SDH) activities were determined histochemically on cryostat sections (tetrazolium method) with quantitative assessment on a spectrophotometer (×280, λ=545 nm) [6]. Immunohistochemical detection of the nuclear antigen of proliferating cells PCNA (DAKO A/S, Denmark, dilution 1:100) was performed on paraffin sections. Statistical data processing was performed using Student's t-test (Statistica for Windows v.6.0). The significance of differences was accepted at $p < 0.05$. The work was carried out in accordance with the ethical principles established by the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (adopted in Strasbourg on 18.03.1986 and confirmed in Strasbourg on 15.06.2006) and approved by the Local Ethics Committee.

RESULTS

In the control group, the stratified squamous non-keratinizing epithelium of the esophagus demonstrated typical architecture: clear stratification into basal, spinous, granular and horny layers, as well as characteristic vertical cellular polarization. Basal cells had a cuboidal or low prismatic shape, basophilic cytoplasm, and an approximately equal ratio of eu- and heterochromatin in the nuclei. Mitotic activity was predominantly localized in the basal layer, appearing as individual foci. The spinous layer was formed by 2–4 rows of polygonal cells with predominance of euchromatin in the nuclei and intense basophilic colour of the cytoplasm. The granular layer consisted of 1–2 rows of flattened cells with pronounced heterochromatin in the nuclei and a large number of basophilic keratohyaline granules in the cytoplasm. The stratum corneum was represented by densely packed horny scales with acidophilic cytoplasm.

Peptide morphogen hydra group

Histological study. In animals receiving PMG, the general structure of the esophageal epithelium was preserved, but statistically significant hyperplasia was observed ($p < 0.001$), mainly due to an increase in the thickness of the spinous layer. The morphology of cells in different layers, including the size of nuclei and the distribution of chromatin, did not visually differ from the control group. At the same time, an increase in the number of mitoses in the basal layer was noted.

Morphometric study. Quantitative morphometric analysis showed an increase in the total thickness of the epithelial layer by 1.4 times ($p < 0.001$) compared to the control group. This increase was mainly due to an increase in the thickness of the spinous layer (1.7 times, $p < 0.001$) and, to a lesser extent, the basal layer (1.3 times, ($p < 0.05$)). The thickness of the stratum corneum did not differ statistically significantly from the controls. Mitotic activity in the basal layer increased by 1.4 times ($p < 0.01$) compared to the controls (Fig. 1). The proliferative index also demonstrated a reliable increase ($p < 0.05$).

*Histochemical study. I*n the control group, NADH-d activity was recorded in all layers of the epithelium, except for the stratum corneum, with uniform distribution of the reaction

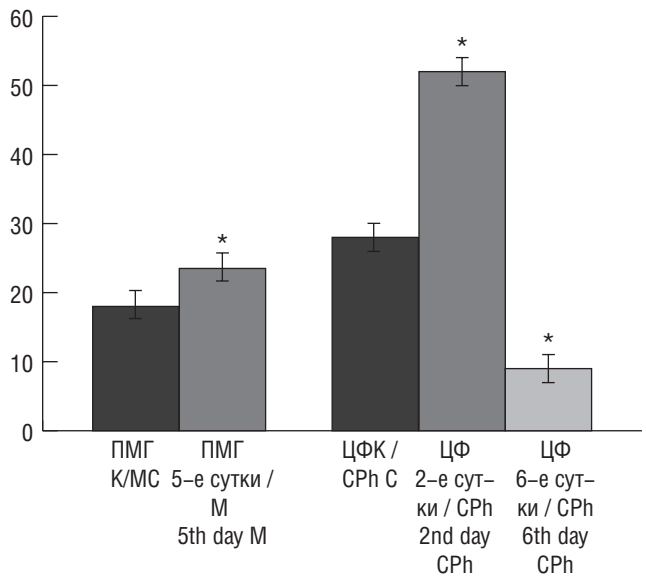

Fig. 1. Mitotic activity in the basal layer of the esophageal epithelium after administration of morphogen (M) and cyclophosphamide (CPh). Ordinate axis: mitotic activity (in ‰). Abscissa axis here and in Figs. 2 — index values: C — control group, 2, 5, 6 — days of the experiment. * Difference from control is significant (p <0,05)

Рис. 1. Митотическая активность в базальном слое эпителия пищевода при введении пептидного морфогена гидры (ПМГ) и циклофосфана (ЦФ). По оси ординат: митотическая активность (в ‰). По оси абсцисс здесь и на рис. 2 — значения показателя: К — контрольная группа, 2, 5, 6 — сутки эксперимента. * Отличие от контроля значимо (p <0,05)

product in the cell cytoplasm. Enzyme activity was higher in the basal layer than in the spinous layer. The introduction of PMG did not change the localization of enzymatic activity, but an increase in the reaction in the basal and spinous layers was visually observed. No significant changes were detected in the stratum corneum and granular layers. Quantitative assessment showed a 1.6-fold increase in NADH-d activity in the basal layer and 1.3-fold in the spinous layer (p <0.01) (Fig. 2). SDH activity also increased significantly (p <0.01) — 1.4 times in the basal layer and 1.5 times in the spinous layer.

Cyclophosphamide group

Histological study. Short-term exposure to high doses of CPh resulted in significant thickening of the epithelial layer already by the second day of the experiment, accompanied by uneven thickening and looseness of the stratum corneum. The overall thickening of the epithelium was statistically significant (p <0.001) and was primarily due to hyperkeratosis. Impaired stratification and differentiation of epithelial cells were observed, with dyskeratosis. Altered relief of the epithelial surface and interstitial edema were observed. Basal cells were randomly located, forming a multi-row layer with variability of basophilic cytoplasm. An increase in the number of cell rows and the volume of epit helial cell cytoplasm were observed in the spinous layer. The size of keratohyaline granules increased in the cells of the granular layer.

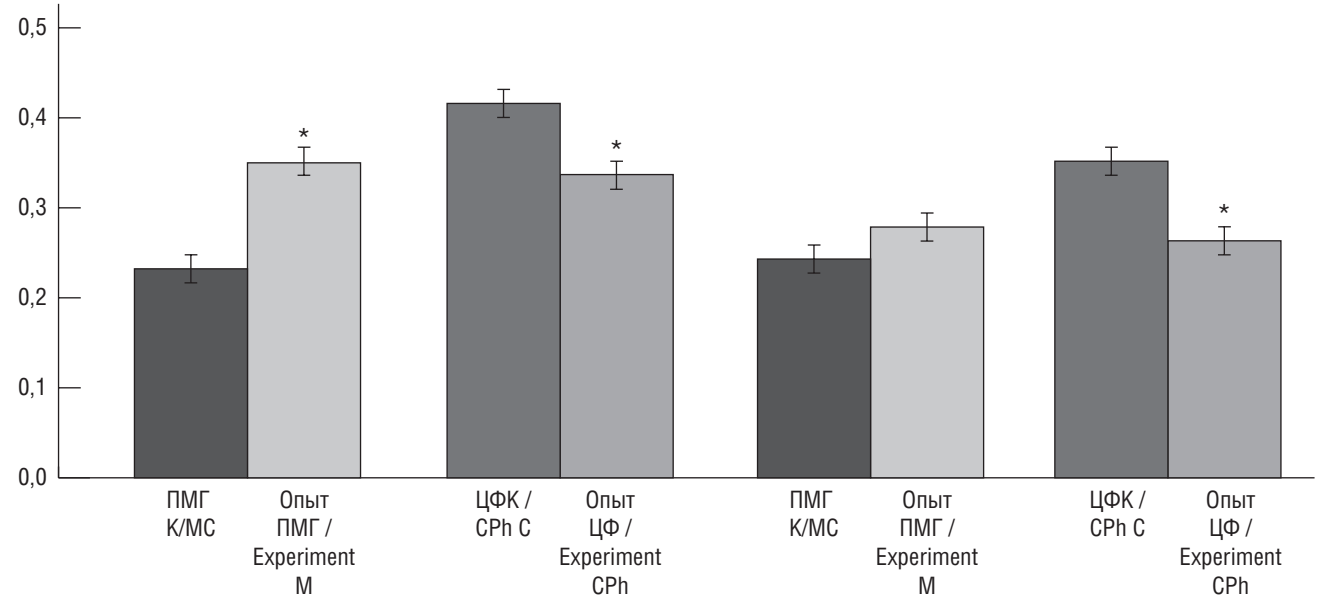

Fig. 2. Activity of NADH diaphorase in the basal (I) and spinous (II) layers of the esophageal epithelium after administration of morphogen (M) and cyclophosphamide (CPh). Ordinate axis: enzyme activity (relative units)

Рис. 2. Активность НАДН-диафоразы в базальном (I) и шиповатом (II) слоях эпителия пищевода при введении пептидного морфогена гидры (ПМГ) и циклофосфана (ЦФ). По оси ординат: активность фермента (отн. ед.)

Morphometric study. The maximum increase in the thickness of the epithelial layer (by 1.7 times) and the thickness of the stratum corneum (by 2.3 times) (Fig. 1) was recorded on the 6th day of the experiment. Mitotic activity after the first injection of CPh increased by 3 times, but by the 8th day it decreased by 1.3 times relative to the control (Fig. 1). The proliferative index showed paradoxical dynamics: the initial increase was replaced by a significant decrease by the end of the experiment ($p < 0.05$).

Histochemical study. NADH-d activity remained relatively stable at the beginning of the experiment, but by the 6th day it decreased by 1.2 times in the basal and spinous layers ($p < 0.01$) (Fig. 2). Similarly, SDH activity in the cytoplasm of spinous cells decreased on average by 1.5 times ($p < 0.01$), which correlates with the suppression of mitochondrial activity under the influence of CPh. *Immunohistochemical study.* Detection of PCNA showed an initial decrease in the number of PCNA-positive cells by 27% relative to the control, followed by an increase of 23% in the basal layer and 99% in the spinous layer on the 6th day.

DISCUSSION

The results demonstrate the antagonistic effect of PMG and CPh on the esophageal epithelium. Since PMG belongs to the class of regulatory neuropeptides [1, 13], it can be assumed that, like other representatives of this class, it is one of the elements of a complex neuropeptide regulatory system that controls various functions of esophageal epithelial cells — proliferation, differentiation, functional activity. This study confirms that PMG induces stimulation of proliferation and metabolism, leading to hyperplasia predominantly in the spinous layer.

The increase in NADH-d activity in the esophageal epithelium after the administration of PMG and the early identified stimulating effect of PMG on SDH activity [3] corresponds to an increase in oxidative metabolism of the tissue.

In general, histological, morphometric and quantitative histochemical data provide grounds to speak about the stimulating effect of PMG on the esophageal epithelium, which is manifested by increased proliferation, general thickening, an increase in the pool of differentiating cells and metabolic activation.

With short-term administration of high doses of CPh, pronounced disturbances in the processes of differentiation and keratinization are observed in the esophageal mucosal epithelium: thickening of the epithelial layer, especially pronounced in the stratum corneum, hyperkeratosis, disturbance of vertical anisomorphism and cytoarchitectonics, such as multi-row arrangement of cells in the basal layer, an increase in the number of rows of epithelial cells in the spinous layer, the appearance of cells with atypical nuclei, an increase in the size of keratohyalin granules in the epithelial cells of the granular layer, loosening of the stratum corneum and its disintegration into complexes of scales, widening of intercellular spaces and interstitial edema. Similar changes have been described in various forms of esophagitis, as well as in foci of esophageal epithelial dysplasia [11, 15]. Morphological changes are accompanied by a decrease in the activity of mitochondrial enzymes NADH-d and SDH, which is consistent with information on the suppression of mitochondrial enzyme activity by cytostatics and the damaging effect of CPh on mitochondria [3–5].

Since CPh is a cytostatic, it could be assumed that its administration would inhibit cell proliferation. However, after the first injection, we, on the contrary, observed a sharp increase in mitotic activity, which can probably be explained by the synchronous completion of mitoses by cells that had already entered the G1 period before the administration of CPh. Perhaps this was also a consequence of the long-term delay of epithelial cells in the S-phase, associated with the alkylating effect of CPh, as well as the processes of reparation of DNA damaged by the cytostatic. This can also explain the decrease in the proportion of PCNA+ cells during this period, since PCNA marks cells in the early S phase and is also a marker of neoplastic transformation of the esophageal epithelium [12]. Decrease of mitotic activity is led by DNA damage of epithelial cells. CPh has cytostatic influence, characterised by hyperkeratosis, impaired differentiation and decreased metabolic activity [8], probably due to mitochondrial dysfunction. The biphasic change in the proliferative response to CPh may be associated with cell cycle synchronization and subsequent cell death.

The obtained results confirm opposite influence of PMG and CPh on epithelial cells of the esophagus. PMG increases proliferation and metabolic function of epithelial cells leading to hyperplasia, predominantly in the spinous layer. This effect is due to the data about regenerative function of PMG. In contrast, CPh causes cytotoxic action, accompanied by hyperkeratosis, differentiation impairment and suppression of metabolic activity, which is probably associated with mitochondrial dysfunction. The initial increase in the proliferative index in the CPh group may be associated with cell cycle synchronization and subsequent cell death.

CONCLUSION

1. The obtained data indicate the opposite effect of PMG and CPh on the morphofunctional characteristics of the esophageal epithelium: PMG stimulates regeneration, while CPh causes damage.

2. The effect of PMG and CPh leads to a pronounced increase in the heteromorphism of the esophageal epithelium.

ADDITIONAL INFORMATION

Authors contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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Experiments with animals. The work was carried out in accordance with the ethical principles established by the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (adopted in Strasbourg on March 18, 1986 and confirmed in Strasbourg on June 15, 2006), and approved by the Local Ethics Committee.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Эксперименты с животными. Работа проведена в соответствии с этическими принципами, установленными Европейской конвенцией по защите позвоночных животных, используемых для экспериментальных и других научных целей (принятой в Страсбурге 18.03.1986 г. и подтверждённой в Страсбурге 15.06.2006 г.) и одобрена Локальным этическим комитетом.

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