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MORPHOFUNCTIONAL CHARACTERISTICS OF THE GLANDULAR EPITHELIUM OF THE ORAL MUCOSA DURING CYTOSTATIC THERAPY

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Abstract. ***Introduction.*** Cytostatic drugs used in oncological practice have a systemic effect on the body, including on the mucous membranes of the gastrointestinal tract, the side effects of which are stomatitis and mucositis, which complicate treatment. ***Objective*** — experimental study of the damaging effect of cytostatic drugs on the glandular epithelium of the oral mucosa and assessment of the reversibility of these changes. ***Materials and methods.*** The epithelium of the minor salivary glands of the tongue was studied on 20 mature white outbred mice after intraperitoneal administration of the cytostatic drug cyclophosphamide at a dose of 400 mg/kg body weight for 5 days. Animals in the control group (20 mice) were injected with isotonic sodium chloride solution at the same frequency. The material was obtained 24 hours and 20 days after the last injection of the drug. Histological and histochemical methods were used. Histochemical studies revealed the activity of the enzyme succinate dehydrogenase in the epithelial cells of the secretory portions of the minor salivary glands, the content of total proteins in serocytes, and the content of glycoproteins and glucosaminoglycans in mucocytes. ***Results.*** Exposure to cyclophosphamide led to a decrease in the activity of cyclophosphamide in serocytes and mucocytes, a decrease in the concentration of proteins in serocytes, and inhibition of the synthesis of glycoproteins and glucosaminoglycans in mucocytes. The changes were reversible. ***Conclusions.*** Cytostatic therapy causes damage to the glandular epithelium of the oral mucosa, which is expressed in the suppression of metabolic and synthetic processes. Serocytes are more sensitive to cytotoxic action than mucocytes. There was a high degree of regeneration of the glandular epithelium of the oral mucosa after the withdrawal of the cytostatic drug.

Keywords: oral cavity, mucous membrane, glandular epithelium, minor salivary glands, cyclophosphamide

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МОРФОФУНКЦИОНАЛЬНАЯ ХАРАКТЕРИСТИКА ЖЕЛЕЗИСТОГО ЭПИТЕЛИЯ СЛИЗИСТОЙ ОБОЛОЧКИ ПОЛОСТИ РТА ПРИ ВВЕДЕНИИ ЦИТОСТАТИКА

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Резюме. ***Введение.*** Цитостатические препараты, применяемые в онкологической практике, оказывают системное воздействие на организм, в том числе и на слизистые оболочки желудочно-кишечного тракта, побочными эффектами которых являются стоматит и мукозит, затрудняющие проведение лечения. ***Цель исследования*** — экспериментальное изучение повреждающего действия цитостатических препаратов на железистый эпителий слизистой оболочки полости рта и оценка обратимости этих изменений. ***Материалы и методы.*** Эпителий малых слюнных желез языка исследовали у 20 половозрелых белых мышей после внутрибрюшинного введения цитостатического препарата циклофосфана в дозе 400 мг/кг массы тела течение 5 дней. Животным контрольной группы (20 животных) через те же промежутки времени вводили изотонический раствор натрия хлорида. Материал получали через 24 часа после последнего введения препарата, а также с целью изучения обратимости изменений, через 20 суток. Применяли гистологический и гистохимический методы. Гистохимические исследования выявляли активность фермента сукцинатдегидрогеназы (СДГ) в эпителиоцитах концевых отделов малых слюнных желез, содержание суммарных белков в сероцитах, а также содержание гликопротеинов и глюкозаминогликанов в мукоцитах. ***Результаты.*** Воздействие циклофосфана приводило к снижению активности СДГ в сероцитах и мукоцитах, уменьшению концентрации белков в сероцитах, угнетению синтеза гликопротеинов и глюкозаминогликанов в мукоцитах. Нарушения были обратимыми, и показатели вернулись к контрольным значениям в конце эксперимента. ***Выводы.*** Терапия цитостатиками вызывает повреждение железистого эпителия слизистой оболочки полости рта, которое выражается в угнетении метаболических и синтетических процессов. Сероциты более чувствительны к цитотоксическому действию, чем мукоциты. На фоне прекращения терапии наблюдалась высокая степень регенерации железистого эпителия слизистой оболочки полости рта.

Ключевые слова: полость рта, слизистая оболочка, железистый эпителий, малые слюнные железы, циклофосфан

INTRODUCTION

Cytostatic drugs used in oncological practice [1, 2] exert a systemic effect on the body, including the mucous membranes of the gastrointestinal tract [3–5]. Side effects such as stomatitis and mucositis are common complications of chemotherapy, significantly impairing patients' quality of life and complicating treatment regimens. Damage to the oral mucosa leads to xerostomia, which causes significant physical discomfort and compromises the suprapepithelial protective mechanisms of the oral mucosa (OM), thereby predisposing patients to infectious complications. The minor salivary glands of the oral cavity are primarily located in the submucosa. They are classified into three types: serous, mucous, and mixed. The secretory end pieces of serous glands consist of serous cells (serocytes), those of mucous glands are composed of mucous cells (mucocytes), while mixed glands contain both cell types [6].

AIM

The aim of this study was to experimentally investigate the damaging effect of cytostatic drugs on the glandular epithelium of the oral mucosa (OM) and assess the reversibility of these changes.

MATERIALS AND METHODS

The study utilized 40 female outbred white mice weighing 23–25 g. Animals in the experimental group (n=20) received intraperitoneal injections of the alkylating cytostatic agent cyclophosphamide (CF, LENS-Pharm, Russia) at a dose of 400 mg/kg body weight every 48 hours for 5 days. Control group animals (n=20) were administered isotonic sodium chloride solution following the same schedule. The investigation focused on the minor salivary glands of the tongue. Tissue samples (tongue) were collected 24 hours after the third CF injection. To assess the reversibility of CF-induced changes, additional samples were obtained 20 days following the final drug administration.

The study targeted the ventral tongue mucosa. *Conventional histological analysis* was carried out on transverse sections stained with hematoxylin and eosin. *Histochemical and cytophotometric analyses* included the detection of total proteins using tetrazolium reactions for histidine, tyrosine, and tryptophan (Burstone's method), glycosaminoglycans with Alcian blue (pH 2.7), and glycoproteins via the periodic acid-Schiff (PAS) reaction in paraffin-embedded sections. Succinate dehydrogenase (SDH) activity was determined in cryostat sections using Lloyd's tetrazolium method. Quantitative cytophotometric analysis of histochemical reactions was performed using a plug-in spectrophotometer, with results expressed as relative optical density units. Statistical analysis was conducted using Statistica for Windows v6.0. Intergroup differences were assessed by Student's t-test, with $p < 0.05$ considered statistically significant. The study complied with the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (Strasbourg, March 18, 1986; revised June 15, 2006) and was approved by the Local Ethics Committee.

RESULTS

Histological analysis demonstrated a reduction in the volume of secretory end pieces in both serous and mucous glands of the tongue, along with decreased size of their constituent serocytes and mucocytes. These findings were supported by quantitative histochemical data, which revealed: a reduction in total protein content within serous cells (from 0.32±0.02 to 0.21±0.03 relative units, RU; Fig. 1), along with suppressed glycoprotein synthesis (Fig. 2) and decreased glycosaminoglycan levels in mucous cells (from 0.55±0.05 to 0.42 ± 0.02 RU and from 0.30±0.02 to 0.22±0.02 RU, respectively). SDH activity decreased from 0.32±0.02 to 0.21±0.02 RU in serocytes (Fig. 3) and from 0.41±0.02 to 0.36±0.01 RU in mucocytes.

By day 20 after treatment cessation, total protein concentration, glycoprotein and glycosaminoglycan levels, and SDH activity in both serous and mucous cells had returned to baseline control values.

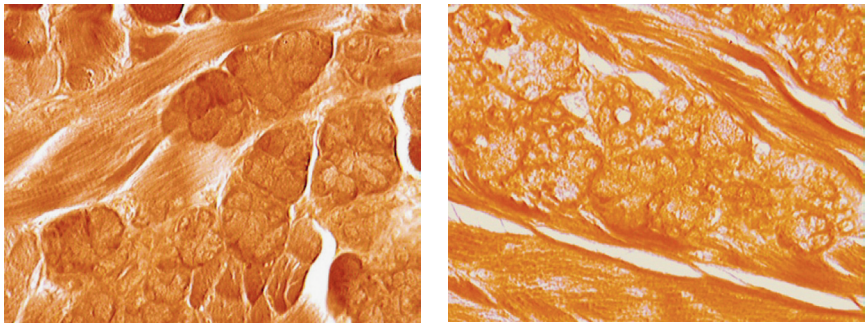
DISCUSSION

Structural changes in the minor salivary gland epithelium accompanied by suppressed synthetic and metabolic activity were observed, indicating high susceptibility to cytotoxic damage from chemotherapeutic agents. These findings correlated with reported data on major salivary gland damage during cytostatic therapy [7, 8]. The resulting xerostomia compromises the protective mechanisms of the OM. Our data revealed more pronounced structural and functional impairment in serocytes than in mucocytes, consistent with the previously reported preferential damage to serous cells in major salivary glands during chemotherapy [8]. Comparative analysis of metabolic and synthetic process disturbances in glandular epithelium versus previously identified disturbances in the surface epithelium of the OM [9] demonstrated that changes in the surface epithelium were less pronounced than in glandular epithelium.

The post-treatment recovery period showed normalization of morphofunctional parameters in the glandular epithelium of the OM, indicating its high regenerative capacity.

CONCLUSION

1. Our findings demonstrate that cytostatic therapy induces damage to the glandular epithelium of the OM, manifesting as suppression of both metabolic and synthetic processes.



а/a *б/b*

Fig. 1. **Secretory portions of protein salivary glands of the tongue: *a* — control group; *b* — after three injections of cyclophosphamide. Reduction of protein content in serocytes. Histochemical detection of total proteins, ×400**

Рис. 1. **Концевые отделы белковых слюнных желез языка: *а* — контрольная группа; *б* — после трех инъекций циклофосфана. Снижение содержания белков в сероцитах. Гистохимическое выявление суммарных белков, ×400**

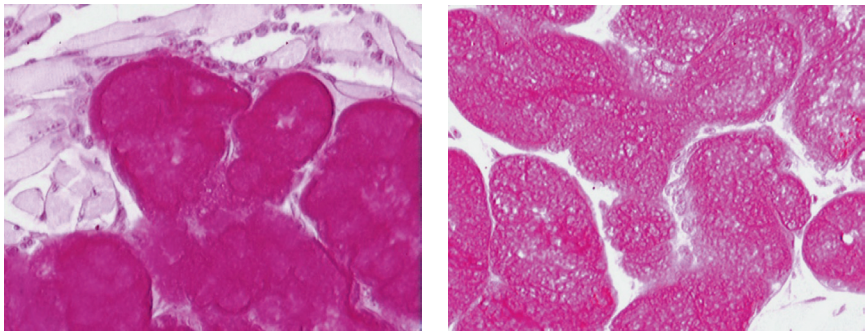


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Fig. 2. **Secretory portions of mucous salivary glands of the tongue: *a* — control group; *b* — after three injections of cyclophosphamide. Reduction in the content of glycoproteins in mucocytes. PAS reaction, ×400**

Рис. 2. **Концевые отделы слизистых оболочек слюнных желез языка: *а* — контрольная группа; *б* — после трех инъекций циклофосфана. Снижение содержания гликопротеинов в мукоцитах. ШИК-реакция, ×400**

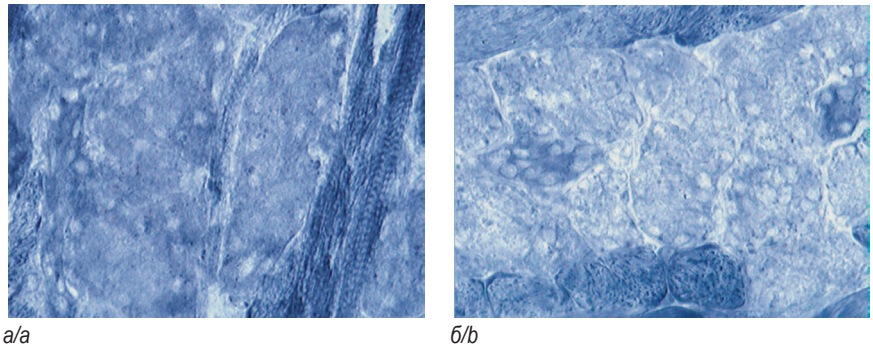

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Fig. 3. **Secretory portions of protein salivary glands of the tongue: *a* — control group; *b* — after three injections of cyclophosphamide. Decreased cyclophosphamide activity in serocytes. Histochemical detection of cyclophosphamide, ×400**

Рис. 3. **Концевые отделы белковых слюнных желез языка: *а* — контрольная группа; *б* — после трех инъекций циклофосфана. Снижение активности сукцинатдегидрогеназы в сероцитах. Гистохимическое выявление сукцинатдегидрогеназы, ×400**

2. Serous cells show significantly greater sensitivity to cytotoxic effects compared to mucous cells.

3. There was a high degree of regeneration of the glandular epithelium of the OM after the withdrawal of the cytostatic drug.

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.

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.

Funding source. This study was not supported by any external sources of funding.

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.

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