Electronic microscopic research on periodont in experimental two-weight opioid action and after its over for four weeks

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Due to the harmful effects of opioid agents in the uncontrolled use of them, it is impossible to ease the early manifestations of damage to the tissues and organs of the oral cavity, which is a pressing problem of today. The purpose of this work was to investigate the features of the sub-microscopic organization of the structural components of the periodontium under the action of an opioid analgesic for two weeks and its four-week withdrawal in the experiment. The study was conducted on 22 adult rats-males of the Wistar line, weighing 160 g, 4.5-6 months of age. Animals were administered intramuscularly daily, once a single opioid analgesic nalbuphine for the first two weeks, in terms of the mean therapeutic dose for the rat, as well as for the mean weight of the test group (0.212 mg/kg), and subsequent four weeks. The fragments of soft periodontal tissue were used for electron microscopic examination. Submicroscopically expressed destructive changes in periodontal tissues were not observed. However, the positive dynamics of regeneration of periodontal components at the ultrastructural level were also not revealed. In the cytoplasm of cells of the epithelium of the free part of the gums, there is destruction of organelles, partially damaged mitochondrial cristae, poorly contoured tonofilaments, shallow karyolemma invaginations, thickened areas and damaged desmosomal contacts. In the surface areas of the periodontium, the collagen fibers are partially stratified, there is moderate swelling of the intercellular substance of the connective tissue, part of the fibrocytes invaginating the karyolemma of the nucleus and placement of heterochromatin in the periphery. Ultrastructurally in the cytoplasm of the macrophage, lysosomes are detected, phagosomes are scarce, indicating a slight damage to the structures. In the gaps of the blood capillaries, blood cells are formed, mainly erythrocytes, in the perinuclear part of the cytoplasm of organelles are few, mitochondria with electron-light matrix and small cristae, perivascular edema is insignificant, there are destructively altered mitochondria in the cytoplasm of endothelial cells of venules, the basement membrane is thickened, the perivascular spaces are enlarged. Thus, at the end of the sixth week of the experiment, no short-term irreversible changes in the ultrastructural organization of the periodontal components were detected in the short-term effect of the opioid for two weeks and its subsequent four-week cancellation. However, the complete restoration of the structural components of the periodontium is not observed, there are signs of reactive changes, reparative processes are slowed.

**Keywords:** periodontium, opioid, abolition of the opioid, ultrastructure, experiment.

**Introduction**

The tissues and organs of the oral cavity are especially responsive to any harmful stimuli in the body [9, 18, 26]. Under the influence of factors of exogenous origin disturbances of gums resistance arise, which causes pathological changes in periodontium tissues [14, 19]. It should be noted that periodontium diseases and gums bleeding are more common in drug abusers compared to the general population [10, 20, 21, 25]. Important are the issues of therapeutic tactics of inflammatory periodontal diseases in drug addicts, as well as the abolition of the drug, which is necessary for both local and general action on the tissues of the periodontal complex [5, 6, 16, 21, 23]. However, the mapping of the pathomorphological pattern in periodontal tissues is a rather complicated process and
changes in this case occur over a period of time with the involvement of different mechanisms of pathogenesis [3, 7]. Therefore, experimental studies related to the study of the ultrastructural organization of the periodontium and the correction of pathological changes that occur during the action of opioids are particularly important today and will help to develop an adequate scheme of corrective effects to stabilize the morphofunctional condition of periodontium tissues.

The aim of the study was to determine the features of the submicroscopic organization of the structural components of the periodontium under the action of an opioid analgesic for two weeks and its four-week withdrawal in the experiment.

Materials and methods
The study was conducted on 22 adult rats-males of the Wistar line, weighing 160 g, aged 4.5-6 months. Animals were divided into 2 groups. The first group included intact rats (n=10). The second group included 12 animals, which were administered intramuscularly opioid analgesic nalbuphine daily for the first two weeks, based on the mean therapeutic dose for the rat, and considering the mean weight of the experimental group (0.212 mg/kg) and its subsequent 4 weeks. Controls were 3 male rats administered intramuscularly saline. Sampling was performed after 6 weeks of the experiment.

All animals were kept under standard vivarium conditions and all experiments were carried out in accordance with the provisions of the “European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes” (Strasbourg, 1985). Before sampling the biopsy material, the animals were primed with intraperitoneal administration of sodium thiopental (25 mg/kg).

For electron microscopic examination, pieces of soft periodontal tissue were used in the gums papilla. The tissue fragments were fixed in a 2.5 % solution of glutaraldehyde and in a 1 % solution of osmium tetroxide on phosphate buffer pH = 7.2-7.4, dehydrated in alcohols and propylene oxide and poured into a mixture of epoxy resins with araldite [24]. Ultra-thin sections were made on a UMPT3m ultramicrotome, which was counterstained with uranyl acetate and lead citrate and studied in a PEM-100-01 electron microscope.

Results
Electron microscopic studies have shown that the structural changes in the epithelium of the different sites studied were similar in nature, but not as significant as in the subgroup of animals without opioid withdrawal. The cells of the basal layer of the epithelial plate of its free part have an enlarged nucleus area, the karyoplasm of which includes the osmiophilic regions of heterochromatin, but they are located mainly near the nuclear envelope. Small, compact nucleolus are available. The karyollemma has shallow invaginations, and its perinuclear spaces are enlarged only in some places. In the cytoplasm there is a normalization of organelles, damaged ultrastructures are small in number. Part of the mitochondria has a focal electron-light matrix and partially damaged cristae. In the hyaloplasm, areas with poorly contoured tonofilaments were detected, some of them homogenized. Thick areas with fuzzy intercellular contacts (Fig. 1) are noted between plasmalemmas. The epitheliocytes of the spinosum and granulosum layers are also less altered, the structure of the nucleus and cytoplasm normalizing.

The nuclei have a shallow invagination of the karyolemma, euchromatin predominates in the karyoplasm. There are different sizes of cells in the granular layer, sometimes large clumps of keratohyalin. The desmosomal contacts are sometimes damaged. The
The ultrastructural organization of the gums epithelium of this group is also unchanged. There is no swelling of the cytoplasm of the epitheliocytes of the basal and spinosum layers. Only the nuclei of the superficial layers of cells have karyolemma invaginations, and the cytoplasm is virtually unchanged. Clear contours of plasmolemma and desmosomal contacts (Fig. 2). Submicroscopically, the epithelium of the attached part of the gums of the animals is found to be unaltered. Epitheliocytes include the oblong-shaped nucleus with shallow invasions of the karyolemma, and euchromatin is noted in the karyoplasm. In the cytoplasm, there are small mitochondria, a few cristae. The clear contours of the plasmolemma, the intercellular contacts are osmiophilic, appear enlarged (Fig. 3).

Electron microscopic studies of the periodontium of animals have found that its structural components are unchanged. Collagen fibers are characterized by a tufted arrangement of fibrils, only in the superficial area they are partially stratified and moderate swelling of the amorphous component of the intercellular substance of the connective tissue is present. Fibroblasts of the usual structure, and some fibrocytes have irregular shape with invaginations of karyolemma of the nucleus and placement of heterochromatin on the periphery. The cytoplasm contains ribosomes, enlarged tubules of the granular endoplasmic reticulum, part of the mitochondria with the enlightened matrix (Fig. 4). Lymphocytes, neutrophils and macrophages are observed in connective tissue surrounding the periodontium. Ultrastructurally, the cytoplasm of the macrophage reveals lysosomes, a little phagosome, indicating little damage to the structures. Plasmolemma forms protrusion in the form of outgrowths and has the invaginations required for phagocytosis of damaged structures (Fig. 5).

Submicroscopic studies of the mucous membrane of the rats gums of this group found that moderate reactive changes are characteristic of the hemomicrocirculatory bed of the gums. The lumps of the blood capillaries are small, in them the formed elements of blood, mainly erythrocytes are found. The nucleus and cytoplasm of endothelial cells have their own structural organization. In the wide cytoplasmic areas of the cells, there are many foam pinocytosis vesicles, caveolae.

In the perinuclear part of the cytoplasm organelles are small in number. The tubules of the endoplasmic reticulum are moderately dilated, mitochondria with electron-light matrix and small cristae. The elongated nucleus is well contoured, the perinuclear spaces are small, and...
**Discussion**

In the modern professional literature there are more and more studies devoted to the study of the effect of opioid drugs on various organs and systems \([1, 8, 12, 17, 22]\), but their effect on the structural organization of the oral cavity and periodontium remains unknown \([6, 10, 20, 21]\). Scientific research is mainly aimed at studying the changes in the internal organs that develop as a result of the introduction of such classic opioids as morphine, tramadol and codeine using significantly high doses \([4, 5, 8, 15]\). In addition, studies on the effects of the opioid analgesic nalbuphine on tissues and organs of the oral cavity are virtually absent in the literature. Preferably, such studies have been performed to study the characteristics of pharmacodynamics and pharmacokinetics both in experiment and in volunteers \([2, 11, 13]\).

As a result of our studies of the experimental effect of opioid for two weeks and its 4-week cancellation, we found no significant destructive changes in periodontium. However, the positive dynamics of regeneration of periodontal components at the ultrastructural level were also not observed. Submicroscopically, there are reactive changes, which are manifested by focal sites of expansion of perinuclear spaces, fuzzy intercellular contacts, partial damage of the cristae in the mitochondria of epitheliocytes and endothelial cells, as well as swelling of the intercellular substance and minor constituents of periodontium.

In the available medical literature there are no results of studies of the ultrastructural organization of periodontal tissues in dynamics at different terms of opioid exposure and after its abolition, which makes it impossible to perform a comparative analysis of the data obtained. Given the relevance of this problem, the study of periodontal tissues in drug addicts is insufficient and requires further scientific research \([5-7, 16, 21, 25]\). Therefore, we believe that the method of creating a biological experimental model of opioid exposure will help to find out the peculiarities of submicroscopic organization in periodontal tissues, which is relevant and necessary in modern dentistry and periodontology.

Prospects for further research are to study the features of ultrastructural reorganization in periodontal tissues when exposed to opioid, after its abolition, and at the application of medical correction at an early date.

**Conclusions**

1. At the end of week 6 of the experiment, no irreversible changes in the ultrastructural organization of periodontal components were detected in the short-term effect of the opioid for two weeks and its subsequent cancellation of.
2. Submicroscopically, it was found that the abolition of opioid analgesic at longer periods (3-6 weeks) does not lead to complete restoration of the structural components of the periodontium, regenerative processes are slow, there are signs of reactive changes.
Відомо, що після відміни впродовж чотирьох тижнів впливає на швидкість вплив опіоїдних речовин при неконтрольованому їх вживанні, неможливо легковажити ранньою промивців ушкоджень тканин і органів ротової порожнини, що складає актуальну проблему сьогодення. Метою цієї роботи було дослідити особливості субміcroскопічної організації структурних компонентів пародонту при дії опіоїдного аналгетика впродовж двох тижнів та його 4-тижневої відміни в експерименті. Дослідження проведено на 22 статевозрілих щурах.

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самцях лінії Wistar, масою 160 г, віком 4,5-6 місяців. Тваринам протягом перших двух тижнів вводили щоденно внутрішньом'язово одноразово опіоїдний аналгетик налбуфін у перерахунку середньої терапевтичної дози для щура, а також з урахуванням середньої ваги піддошлікої групи (0,212 мг/кг) та іого подальшою відміною протягом наступних 4 тижнів. Для електронно-мікроскопічного дослідження використали фрагменти м'яких тканин пародонту. Субмікроскопічно виражених деструктивних змін у тканинах пародонту виявлено не було. Позитивної динамики регенерації компонентів пародонту на ультраструктурному рівні також не виявили. У поверхневих ділянках капланові волокна були частково розщущеною і спостерігали помірні графіти міжплазмічної речовини. У частини фіброцитів виявлено включення каріолеми ядра та розширення гетерохроматину на периферії. Ультраструктурно у цитоплазмі макрофага відмічено гіпокінез доні і збільшення дистрофічних змін. Позитивної динамики регенерації компонентів пародонту не виявили. Слід зазначити, що повного відновлення структурних компонентів пародонту не спостерігався, наявні ознаки реактивних змін, репаративні процеси сповільнені.

Ключові слова: пародонт, опіоїд, відміна опіоїду, ультраструктура, експеримент.

Учитывая вредное воздействие опиоидных веществ при неконтролируемом их употреблении, невозможно пренебрегать ранними проявлениями повреждений тканей и органов ротовой полости, что составляет актуальную проблему современности. Целью работы было исследовать особенности субмикроскопической организации структурных компонентов пародонта при действии опиоидного анальгетика в течение двух недель и после его 4-недельной отмены в эксперименте. Исследование проведено на 22 половозрелых крысах-самцах линии Wistar, массою 160 г, в возрасте 4,5-6 месяцев. Животным в течение первых двух недель вводили ежедневно внутримышечно однократно опиоидный анальгетик налбуфін в перерасчете средней терапевтической дозы для крысы, а также с учетом среднего веса подопытной группы (0,212 мг/кг) и его последующей отменой в течение следующих 4 недель. Для электронно-мікроскопического исследования использовали фрагменты мягких тканей пародонта. Субмікроскопічно виражених деструктивних змін в тканинах пародонта виявлено не було. Положительной динамики регенерации компонентов пародонта на ультраструктурном уровне также не вишило. Положительной динамики регенерации компонентов пародонта в течение двух недель и после его 4-недельной отмены в эксперименте. В просветах кровеносных капилляров выявляются форменные элементы крови, преимущественно эритроциты, в перинуклеарной части цитоплазмы наблюдали деструктивные изменения, частично поврежденные ядра митохондрий, плохо контурировались тонкоилюменты, установлены глубокие изменения каріолеммы, между плазмамеммами наблюдали утолщенные участки и поврежденные десмосомальные контакты. В поверхностных участках периодонта капланові волокна были частично расслоенными, наблюдали умеренный отек межклеточного вещества соединительной ткани, в части фіброцитов установлены утолщенные каріолеммы и наличие гетерохроматинна на периферии. Ультраструктурно в цитоплазме макрофага отмечены лизосомы, фагосом немного, что свидетельствует о незначительном повреждении структур. В просветах кровеносных капилляров выявляются форменные элементы крови, преимущественно эритроциты, в перинуклеарной части цитоплазмы наблюдали деструктивные изменения митохондрии, базальная мембрана утолщена, периваскулярные пространства увеличены. Таким образом, в конце 6 недели эксперимента при кратковременном действии опиоида в течение двух недель и его дальнейшей 4-недельной отмены, глубоких ноаребных изменений ультраструктурной организации компонентов пародонта не наблюдалось, в наличии явные признаки реактивных изменений и замедленные репаративные процессы.

Ключевые слова: пародонт, опиоїд, відміна опіоїду, ультраструктура, експеримент.

ЭЛЕКТРОННО-МИКРОСКОПИЧЕСКИЕ ИССЛЕДОВАНИЯ ПАРОДОНТА ПРИ ЭКСПЕРИМЕНТАЛЬНОМУ ДВУХНЕДЕЛЬНОМ ВЛИЯНИИ ОПИОИДА И ПОСЛЕ ЕГО ОТМЕНЫ В ТЕЧЕНИЕ ЧЕТЫРЕХ НЕДЕЛЬ

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Учитывая вредное воздействие опиоидных веществ при неконтролируемом их употреблении, невозможно пренебрегать ранними проявлениями повреждений тканей и органов ротовой полости, что составляет актуальную проблему современности. Целью работы было исследовать особенности субмикроскопической организации структурных компонентов пародонта при действии опиоидного анальгетика в течение двух недель и после его 4-недельной отмены в эксперименте. Исследование проведено на 22 половозрелых крысах-самцах линии Wistar, массою 160 г, в возрасте 4,5-6 месяцев. Животным в течение первых двух недель вводили ежедневно внутримышечно однократно опиоидный анальгетик налбуфін в перерасчете средней терапевтической дозы для крысы, а также с учетом среднего веса подопытной группы (0,212 мг/кг) и его последующей отменой в течение следующих 4 недель. Для электронно-микроскопического исследования использовали фрагменты мягких тканей пародонта. Субмікроскопічно виражених деструктивних змін в тканинах пародонта виявлено не було. Положительной динамики регенерации компонентов пародонта на ультраструктурном уровне также не вишило. Положительной динамики регенерации компонентов пародонта в течение двух недель и после его 4-недельной отмены в эксперименте. В просветах кровеносных капилляров выявляются форменные элементы крови, преимущественно эритроциты, в перинуклеарной части цитоплазмы наблюдали деструктивные изменения, частично поврежденные ядра митохондрий, плохо контурировались тонкоилюменты, установлены глубокие изменения каріолеммы, между плазмамеммами наблюдали утолщенные участки и поврежденные десмосомальные контакты. В поверхностных участках периодонта капланові волокна были частично расслоенными, наблюдали умеренный отек межклеточного вещества соединительной ткани, в части фіброцитов установлены утолщенные каріолеммы и наличие гетерохроматинна на периферии. Ультраструктурно в цитоплазме макрофага отмечены лизосомы, фагосом немного, что свидетельствует о незначительном повреждении структур. В просветах кровеносных капилляров выявляются форменные элементы крови, преимущественно эритроциты, в перинуклеарной части цитоплазмы наблюдали деструктивные изменения митохондрии, базальная мембрана утолщена, периваскулярные пространства увеличены. Таким образом, в конце 6 недели эксперимента при кратковременном действии опиоида в течение двух недель и его дальнейшей 4-недельной отмены, глубоких ноаребных изменений ультраструктурной организации компонентов пародонта не наблюдалось, в наличии явные признаки реактивных изменений и замедленные репаративные процессы.

Ключевые слова: пародонт, опиоїд, відміна опіоїду, ультраструктура, експеримент.