

РЕЗЮМЕ

РОЛЬ ОКСИДА АЗОТА И РЕОЛОГИЧЕСКИХ СВОЙСТВ КРОВИ В ПОДДЕРЖАНИИ ТЕМПЕРАТУРНОГО ГОМЕОСТАЗА В ТКАНИ ГОЛОВНОГО МОЗГА

Джоджуа Н.Н., Гонгадзе Н.В., Митагвария Н.П.

Тбилисский государственный медицинский университет, Центр экспериментальной биомедицины им. И. Бериташвили, Грузия

В экспериментах на белых крысах исследуется проблема регуляции температуры в ткани головного мозга в условиях управляемой гипертермии всего тела. Полученные результаты позволяют утверждать, что головной мозг обеспечен высокоэффективной системой ауторегуляции температуры при экзогенных температурных воздействиях. Верхний предел этой ауторегуляции (для крыс, по крайней мере) находится в пределах 45°C окружающей среды. Важную роль в нормальном функционировании системы ауторегуляции температуры в головном мозгу играет оксид азота. Кроме этого, выявлено, что повышение индекса агрегируемости эритроцитов может существенно сказаться (помимо всего прочего) и на поддержание температурного гомеостаза в головном мозгу.

რეზიუმე

აზოტის ოქსიდის და სისხლის რეოლოგიური თვისებების როლი თავის ტვინის ქსოვილის ტემპერატურული ჰომეოსტაზის შენარჩუნებაში

ნ. ჯოჯუა, ნ. გონგაძე, ნ. მითაგვარია

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, თბილისის ბერიტაშვილის ექსპერიმენტული ბიომედიცინის ცენტრი, თბილისი, საქართველო

ნაშრომში შესწავლილია თეთრი ვირთაგვების თავის ტვინის ქსოვილში ტემპერატურის რეგულაციის საკითხი სხეულის ჰიპერთერმიის პირობებში. მიღებული შედეგებით დგინდება, რომ თავის ტვინი უზრუნველყოფილია ტემპერატურის ავტორეგულაციის ეფექტური სისტემით, რომელიც იცავს მას ეგზოგენური ტემპერატურული ცვლილებებისაგან. ამ ავტორეგულაციის ზედა ზღვარი (ვირთაგვებისთვის) განისაზღვრება გარემოს ტემპერატურის დაახლოებით 45°C-ით. თავის ტვინის ტემპერატურის ავტორეგულაციის სისტემის ნორმალურ ფუნქციონირებაში მნიშვნელოვან როლს ასრულებს აზოტის ოქსიდი. ასევე, დადგენილია, რომ ერითროციტების აგრეგაციის ინდექსის ზრდამ შესაძლოა, სხვათაგან ერთად, მნიშვნელოვნად შეაფერხოს თავის ტვინში ტემპერატურული ჰომეოსტაზის შენარჩუნება.

STRUCTURAL CHANGES IN SUBMANDIBULAR SALIVARY GLAND, CAUSED BY HEAVY METAL SALTS, AND THEIR CORRECTION WITH DIALIPON (EXPERIMENTAL STUDY)

¹Sikora V., ¹Bojko V., ¹Tkach G., ²Kyptenko L., ²Lyndin M.

¹Sumy State University, normal anatomy department with a topographical anatomy and operational surgery course; ²department of pathology, Ukraine

Salivary glands play a considerable role the vital functions of an organism. They provide homeostasis constancy not only of an oral cavity but also of top departments of gastrointestinal tract, executing primary enzymatic food processing, helping the food passing through a gullet. Presumably there are no other organs, that would carry out such a variety of functions (secretory, recretory, excretory, incretory) and would have so much influence to the organism condition, organs of oral cavity and digestive system on the whole, as salivary glands [1].

Frequency of large salivary glands disease in the structure of general pathology is about 0,6-1,5%. Sialolithiasis takes

about 20 - 60%, here the process strikes submandibular salivary gland (SSG) more often (91-95,4%). Men and women can be ill approximately identically. The pathology appears at any age, even from a babyhood [2]. Frequency of tumor development in SSG is not high (4%). Sexual differences in morbidity demonstrate greater frequency of tumour development for men (correlation of men and women - 2,5: 1). Neoplasia is diagnosed between men at age 28-60 (average 42,6), between women at age 40-59 (average 47) [3].

The factors that promote development of disease are: violation of mineral exchange, hypo- and avitaminosis

A, violation of saliva electrolyte composition, violation of enzymatic activity, decline of salivary gland secretory activity, which is followed by saliva condensing, violation of saliva formation with its speed secretion decline, changes in anatomic structure of the gland flowing system, acute and chronic inflammatory processes (chronic sialoadenitis and sialodochitis) etc [4].

However, one of the most essential risk factors of gland disease is a permanent increase of socialdemographic process, which is characterized by increasing number of urban population, growth of chemical and electroenergetical industry, usage of mineral fertilizers, containing metals pesticides, emission of industrial waste in different actual states (hard, liquid, gas and vaporous) and exhaust, low technological level at industrial enterprises [5]. It creates continuous influence of ecosystem on living organisms [6]. As a result, in some regions there are groups of elements that are not natural, and characteristic for the technogenesis [7]. While adapting oneself to the new conditions, protection mechanisms turn on, they can resist to harmful influence of aggressive factors during a certain time [8]. But further there is an exhaustion of reserves, that results in adaptation failure adapting mechanisms are transformed into pathological ones, which affect first at cell and biochemical levels, and eventually become the reason of morphological changes at organ level [9].

Nowadays, heavy metals are basic pollutants of environment, their level exceeds allowable norms in many regions of Ukraine and the world [7]. Increasing content of ions of copper, zinc, iron, manganese, chrome and lead in soil is observed in northern districts of Sumy region. Their concentration exceeds allowable one in 10-100 times [10].

The scientists all over the world pay great value to studying of heavy metals influence to a human's organism and laboratory animals. It is reflected in many works, majority of which specifies negative influence of metals on organs and systems of human organism [11]. The mechanism of heavy metals combination influence consists of a local and resorbitive effects [12]. The local effect is shown in tissues destruction and depends on the capacity of these combinations for dissociation. Thus as a result of proteins compression and denaturation, dystrophic and necrotizing changes in tissue are observed. The cornerstone of the resorbitive effect is blocking of functionally active enzyme groups and structural proteins [13].

There is a number of works in literature which study structural alteration of bones [14], testicles [15], thyroid gland [16], dental enamel [17] on condition of natural and technogenic microelementosis, but there are no scientific works that would light up the complex study of salivary glands morphological changes on condition of combined influence of several microelements.

So, the purpose of our investigation is studying of morphological changes in submandibular salivary gland of animals on condition of heavy metals salts effect and research of correcting influence of medicinal drug Dialipone to structural changes in submandibular salivary gland.

Material and methods. We conducted an experiment at 90 white male-rats of young, mature and advanced age.

All experiments are conducted following the rules of European Convention of Animals Protection [18,19].

Taking into account well-marked antioxidant properties of aliphatic acid, we chose a pharmacological drug "Dialipone" to correct structural alteration in submandibular salivary gland, caused by microelementosis.

Rats were divided in 2 groups control one and experimental one. There were 18 rats of different age in a control group. The rats got normal drinking-water and food according to standard daily rate.

There were 72 rats of young, mature and old age (from 4th to 22th months) in experimental group. This group of rats was divided into 2 groups of 36 animals. The first group drank water with heavy metals salts in concentrations, that are determined in soil and water of some districts of Sumy region (salts of zinc ($ZnSO_4 \times 7H_2O$) – 5 $\mu g/l$ /l, copper ($CuSO_4$ of $x 5H_2O$) - 5 $\mu g/l$ /l, iron ($FeSO_4$) - 10 $\mu g/l$ /l, lead ($Pb(NO_3)_2$) - 3 $\mu g/l$, manganese ($MnCl_2$ of $x 4H_2O$) – 1 $\mu g/l$ /l) [10]. The correction was conducted by Dialipone. The second group drank water with heavy metals salts without any corrector. The first group of animals was divided into 2 subgroups: first one consisted of rats that were taken out of experiment in 1 month; the second subgroup was the animals that received heavy metals salts and the corrector during two months. The second group was divided also into 2 subgroups on the same principle.

The corrector "Dialipone" was slowly injected in an abdominal region once a day in a dose of 60 μg to 1 kg of body weight.

Animals were taken out of the experiment by means of decapitation under aethereal anesthesia.

A part of submandibular salivary gland was taken for the histological research. It was fixed in 10% solution of neutral formalin (during 24 hours). Serial cuts were executed about 7-9 μm each, that passed through a center, subcapsularis and intermediate areas of a gland. Preparations were painted over with a standard methods.

Prepared histological preparations were investigated and photographed by means of the digital image display system "SEO Scan ICX 285 AK-F IEE-1394».

Microsoft Excel 2010 with addition AtteStat 12.0 was used during a statistical research (determination of normal selection by Kolmogorov criterion, calculation of Student independent criterion, Pierson's correlation coefficient - r and reliability of differences - p).

Results and their discussion. After 30 days of combination influence of heavy metals salts and the corrector drug in submandibular salivary gland of young rats one can observe considerably less deviations in linear size and architectonics of gland particles, comparing to the results of control group of animals. During the PAS reaction in gland tissue one can observe intensification of color saturation in epithelial cells, epithelium of the implanted and striated ducts, comparing to the corresponding group of rats that had combination of heavy metals salts only (Fig. 1).

There is an insignificant divergence of collagen fiber, minimum signs of swelling in the capsule and interacinar layers of gland connective tissue. Blood vessels of the capsule are expanded, with increased blood filling, located more compact, compared to the group of microelementosis influence, where in interacinar stroma one can often observe the signs of swelling in the form of cavities.

There is insignificant growth of connective tissue around ducts and in periacinar area in both groups.

After 60-day's experiment with Dialipone in submandibular salivary gland of young rats one can observe insignificant damage of glandular parenchima cells, that showed up in form of small focuses of fatty and albuminous proteinaeous degeneration. Animals of this group, compared to the second group (2 subgroup) of animals of young age,

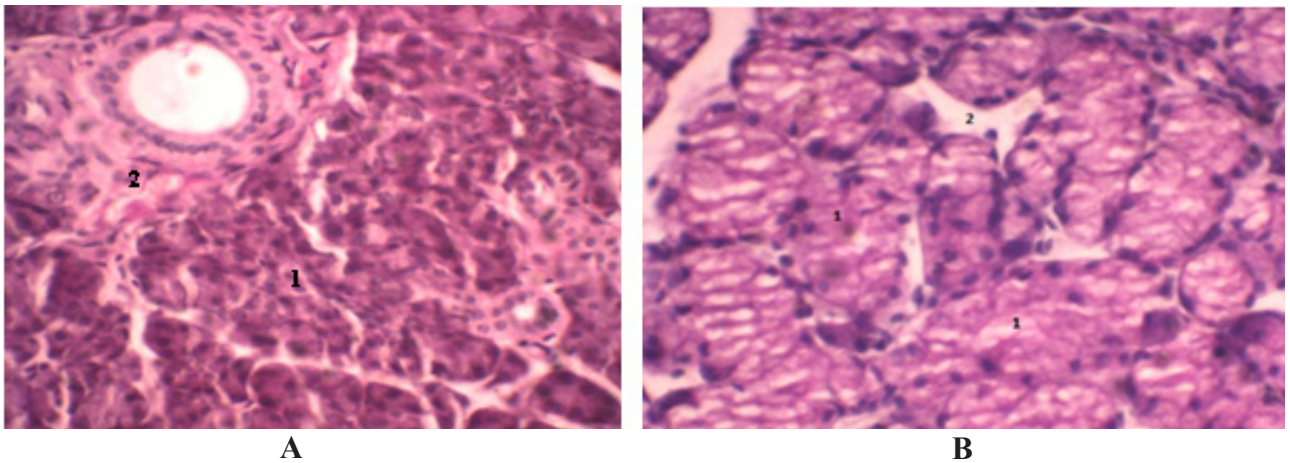


Fig. 1. Submandibular salivary gland of a young rat after 30 days of simulated microelementosis (A) and after 30 days of microelementosis with corrector usage (B). Zoom x 360. Painted over with hematoxylin- eosine.
A: 1 – epithelium of glands with PAS-positive formations.
B: 1 – epithelium of glands with PAS-positive formations, 2 – swallowing

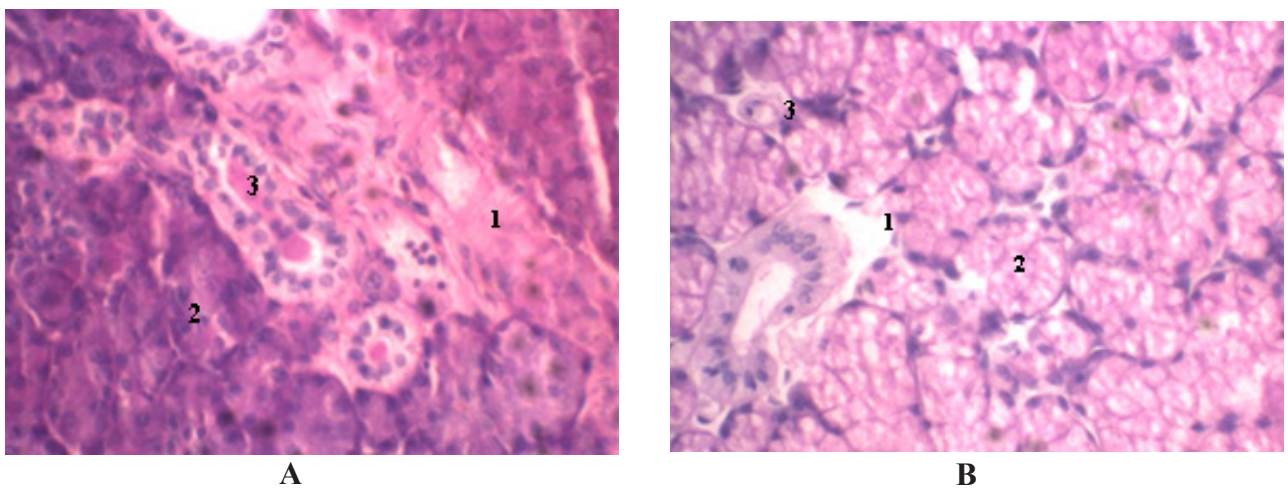


Fig. 2. Submandibular salivary gland of a young rat after 60 days of microelementosis (A) and after 60 days of microelementosis with corrector (B). Zoom x 360. Painted over with hematoxylin- eosine. A: 1 – growth of connective tissue, 2 – epithelium of a duct and particles, 3 – interdact secretion. B: 1 –swallowing, 2 – epithelium of a duct and particles with insignificant quantity of carbohydrate formations, 3 - hemocapillaries

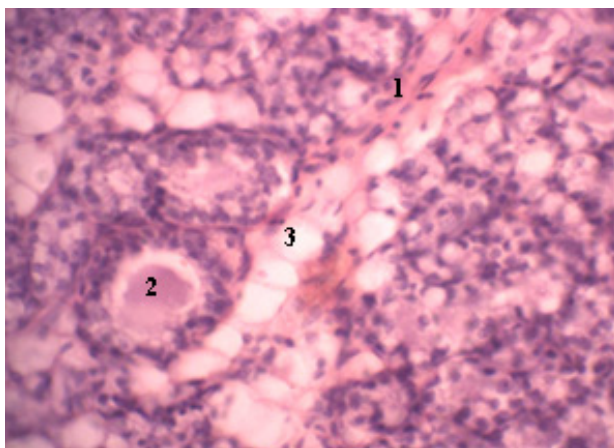
had less distinct dyscirculatory violations. There are signs of swallowing, dilatation and hemocapillar wall bulge in the stroma component (Fig. 2). One can also observe some grows of connective tissue around vessels and ducts.

In general, one can observe better saving of glandular epithelium, less prevalence of dystrophic and discirculatory changes, sclerotization processes in stroma, comparatively to the histological research results of submandibular salivary gland tissue of young animals without the microelementosis influence correction.

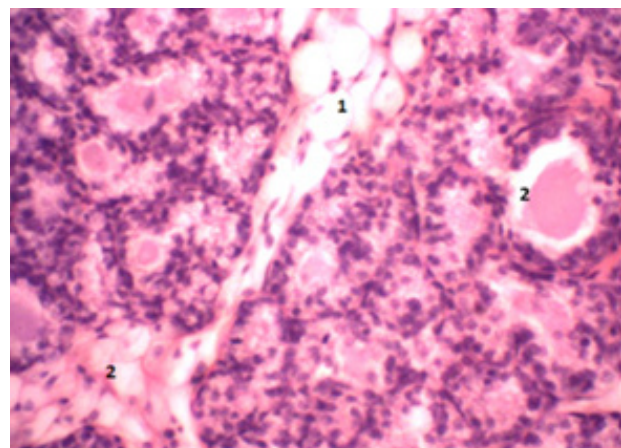
After 30-days joint use of heavy metals salts combination and the corrector there is insignificant amount of cells with fatty and hydropic degeneration in submandibular salivary gland of mature rats. There is a secretion delay, desquamation of some cells (Fig. 3) in gland duct system. Comparing to the group of animals of corresponding age,

which had microelementosis without any corrector, there is more parenchima with signs of glandular epithelium stable functioning, but there is less stroma component. One can observe moderate hemocapillar dilatation, venous congestion, insignificant perivascular stroma swallowing.

After 60-days of correction with Dialopine in submandibular salivary gland of rats of mature age one can observe a tendency to damaged tissue area reduction comparing to the group of animals of corresponding age without corrector use. There are dystrophic changes in some terminal parts. There are some desquamated cells and insignificant secretion accumulation in implanted and striated ducts of the gland. One can observe a phenomenon of implanted ducts branching as a sign of strengthening of regeneration process in submandibular salivary gland. Connective tissue grows mostly perivascular and periductal, interparticle partitions broaden. There is a venous congestion in some small vessels (Fig. 4).

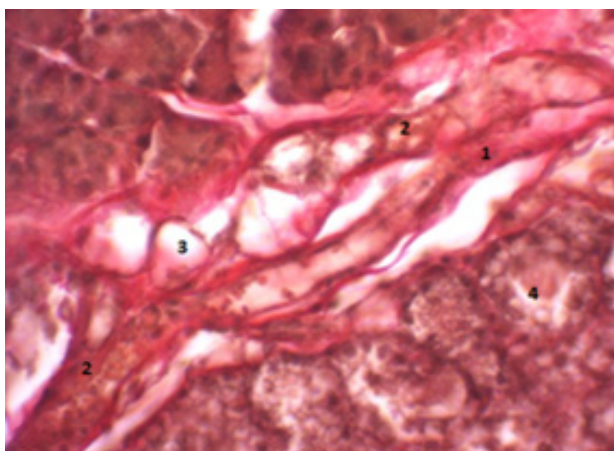


A

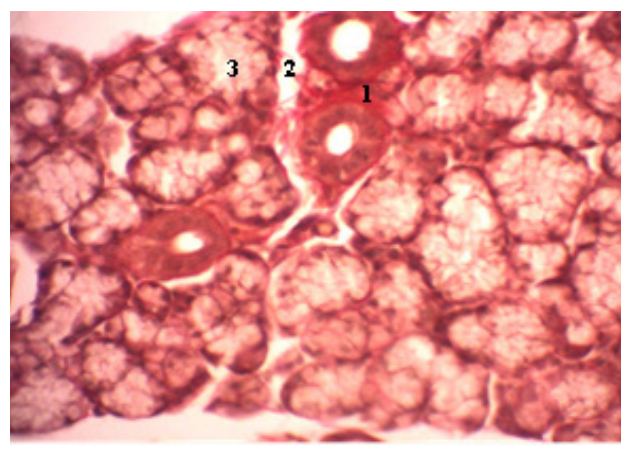


B

Fig. 3. Submandibular salivary gland of a mature rat after 30 days of microelementosis (A) and after 30 days of microelementosis with corrector (B). Zoom x 400. Painted over with hematoxylin- eosine. A: 1 – connective tissue, 2 – intraparticle duct with secretion, 3 – fatty tissue. B: 1 – epithelium of hybrid acinus with areas of stroma fatty degeneration, 2 – secretion retardation in duct clearance

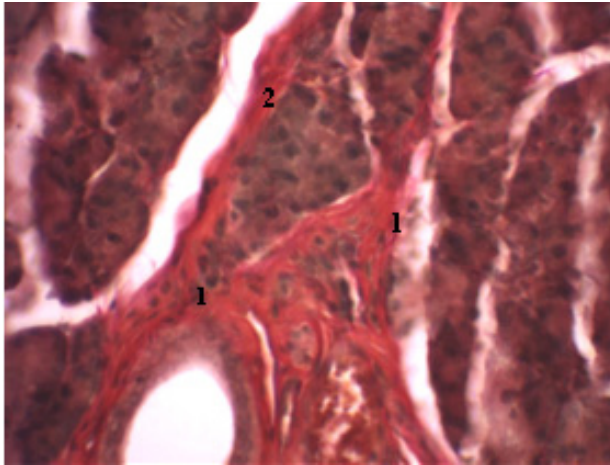


A

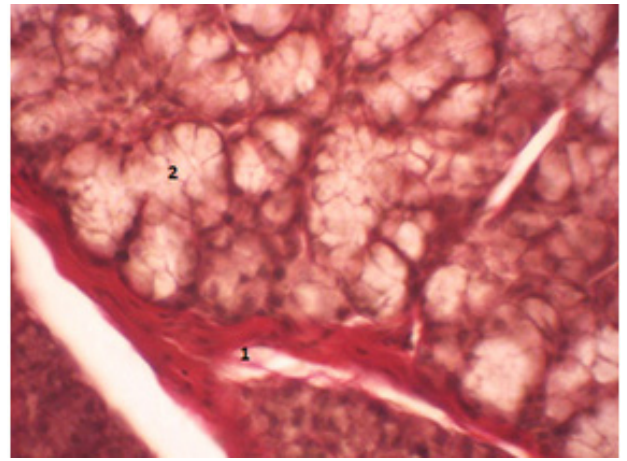


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Fig. 4. Submandibular salivary gland of a mature rat after 60 days of microelementosis (A) and after 60 days of microelementosis with corrector (B). Painted over due to Van-Gizon. Zoom x 400. A: 1 – smooth fibrous connective tissue, 2 – hemocapillaries, 3 – adipocytes, 4 – interaduct with secretion. B: 1 – periductal fibrosis, 2 – swallowing, 3 – acinus with degenerative changes

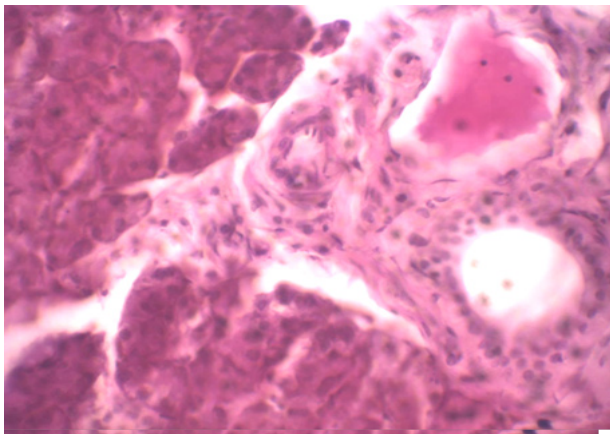


A

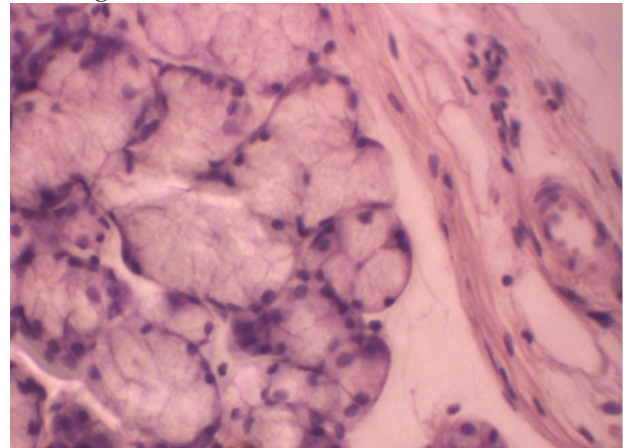


B

Fig. 5. Submandibular salivary gland of a senior rat after 30 days of simulated microelementosis (A) and after 30 days of microelementosis with corrector usage (B). Painted over due to Van-Gizon. Zoom × 400.
A: 1 – periductal, perivascular and ma periacinar connective tissue, 2 – swallowing.
B: 1 – intraparticle connective tissue with swallowing, 2 – mucous terminal sections



A



B

Fig. 6. Submandibular salivary gland of a senior rat after 60 days of microelementosis (A) and after 60 days of microelementosis with corrector usage (B). Zoom × 400. Painted over with hematoxylin- eosine.
A: 1 – acinus epithelium, 2 – periductal fibrosis, 3 – dilatation the duct clearance with secretion reservation.
B: 1– swallowing, 2 – degenerative changes in duct epithelium

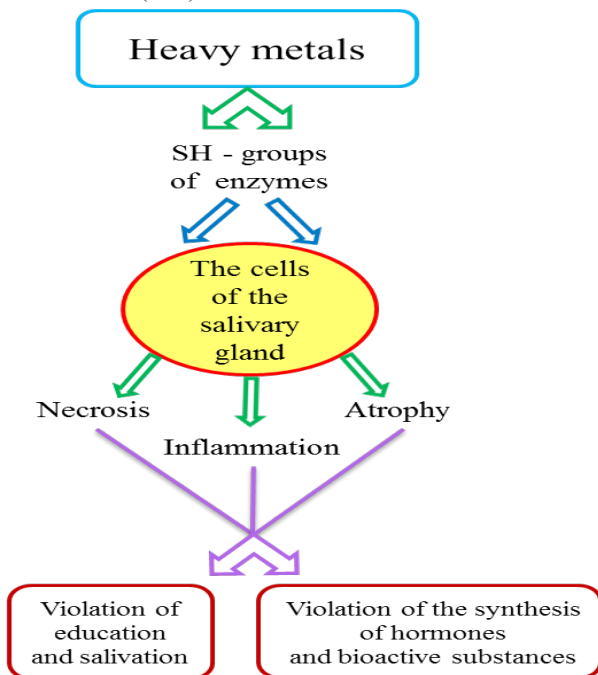
After 30 days' of concurrent taking of heavy metals salts combination and corrector in submandibular salivary gland of senior rats one can observe structure heterogeneity of parenchima: there are some fatty and hydropic degenerations among acinus with kept structure. Mucous terminal parts of glands that prevail in parenchima structure are separated by connective tissue layers with some signs of swallowing (Fig. 5). Comparing to the group of senior rats, which had microelementosis and did not take Dialipone, one can observe the reduction of swallowing, fibrosis changes, dystrophic and atrophic transformations of parenchima.

After 60-days of correction with Dialopine in submandibular salivary gland of old rats one can observe tissue swallowing, granulocyte centers with dystrophic changes. Sometimes glandular cells contain signs of apoptosis. In

general, the area of gland parenchima component diminishes due to atrophic and involutory process. There is an expansion of connective tissue component: interparticle membranes and capsule the amount of connective tissue component grows around large vessels, ducts (Fig. 6). Comparing histological changes to the group of senior animals, which did not take the corrector, one should notice less distributive dystrophic, atrophic and dycirculatory changes.

Without doubts, influence of environment harmful factors, including heavy metals salts, results in structural changes in submandibular salivary gland that leads to to progress of diseases. The inflow of heavy metals in the organ results in substituting of essential macro- and microelements in a cell [20], blocking of active functional groups of enzymes, proteins [21]. The most important is blocking of sulfhydryl

and thiol groups that provide biological activity to over 50% enzyme proteins; amine, carboxyl and other groups are blocked less (Pic.).



Pic. The pathogenesis of the influence of heavy metals in the salivary gland

Thus, experimental animals in the conditions of simulated microelementosis have signs of granulocyte dystrophic and atrophic changes. Coarse-fibred stroma, capilar sclerosis, hemorrhages are observed. During the processes of Dialipone corrective influence, damage of submandibular salivary gland tissue diminished. The swallowing and fibrotic changes were less expressed, as well as dystrophic and atrophic parenchyma transformations.

Except impressive antioxidant properties, the drug has membrane stabilizing, antihypoxic, detoxification effects and activates damaged tissue regeneration.

Conclusions. Research of Dialipone corrective influence on structural changes in submandibular salivary gland of rats of the different age, caused by microelementosis, confirms perspective of the drug application. While comparing restoration possibilities of Dialipone for the gland tissue it was noticed that animals of different ages have got different efficiency of application the corrector.

The rats of young and mature age have got more complete renewal of structural changes. The rats of senior age have got less complete and effective renewal of structure, than young animals, which is explained by worse reparative possibilities for old rats.

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SUMMARY

STRUCTURAL CHANGES IN SUBMANDIBULAR SALIVARY GLAND, CAUSED BY HEAVY METAL SALTS, AND THEIR CORRECTION WITH DIALIPONE (EXPERIMENTAL STUDY)

¹Sikora V., ¹Bojko V., ¹Tkach G.,
²Kyptenko L., ²Lyndin M.

¹Summy State University, normal anatomy department with a topographical anatomy and operational surgery course; ²department of pathology, Ukraine

Setting of possibilities of structural changes correction in submandibular salivary gland with a Dialipone drug, caused by adverse effect of heavy metals salts on an organisms of different age group rats.

Structural changes and their correction were studied on the histological preparations basis painted by hematoxy-

lin-eozin, Van-Gizon, PAS reaction, investigated and photographed by means of the digital image display system "SEO Scan".

In comparison to the results of submandibular salivary gland tissue histological research of animals without any correction of microelementosis, animals that took Dialipone are marked with a better glandular epithelium saving, less widespreading of dystrophic and dyscirculatory changes, sclerotization processes in stroma.

When comparing of Dialipone restoration possibilities, it was set, that different age group animals show different application efficiency of the corrector. The rats of young and mature age have more complete renewal of structural changes. The rats of advanced age show worse reparative capabilities, less complete and effective renewal of structural changes.

Keywords: salivary gland, heavy metals, corrector.

РЕЗЮМЕ

СТРУКТУРНЫЕ ИЗМЕНЕНИЯ В ПОДНИЖНЕЧЕЛЮСТНОЙ СЛЮННОЙ ЖЕЛЕЗЕ, ВЫЗВАННЫЕ СОЛЯМИ ТЯЖЕЛЫХ МЕТАЛЛОВ, И ИХ КОРРЕКЦИЯ С ПОМОЩЬЮ ДИАЛИПОНА (ЭКСПЕРИМЕНТАЛЬНОЕ ИССЛЕДОВАНИЕ)

Сикора В., Бойко В., Ткач Г.,
Киптенко Л., Линдин М.

Сумской государственной университет, Украина

Целью исследования явилось установление возможностей коррекции структурных изменений в поднижнечелюстной слюнной железе препаратом диалипон, которые вызваны вредным воздействием солей тяжелых металлов на организм крыс разных возрастных периодов.

Структурные изменения и их коррекция были изучены на гистологических препаратах, окрашенных гематоксилин - еозином, Ван Гизону, шик-реакцией, которые исследовали и фотографировали с помощью цифровой системы вывода изображения «SEO Scan».

По сравнению с результатами гистологического исследования ткани поднижнечелюстной слюнной железы животных без коррекции под влиянием микроэлементоза у животных, получавших диалипон, отмечается большая сохранность железистого эпителия, меньшая распространенность дистрофических и дисциркуляторных изменений, процессов склеротизации в строме.

При сравнении восстановительных возможностей диалипона установлено, что у животных разных возрастных групп оказывается различная эффективность

действия корректора. У крыс молодого и зрелого возраста происходит полное восстановление структурных изменений. У крыс старческого возраста оказываются

более низкие репаративные возможности, восстановление структуры менее полное и эффективное, чем у животных младших возрастных групп.

რეზიუმე

პრეპარატ დიალიპონის კორექციული ეფექტი ქვედა ყბისქვეშა სანერწყვე ჯირკვლის სტრუქტურულ ცვლილებებზე მძიმე მეტაბოლური ზემოქმედების პირობებში (ექსპერიმენტული კვლევა)

ვ. სიკორა, ვ. ბოიკო, გ. ტაჩი, ლ. კიპტენკო, მ. ლინდინი

სუმის სახელმწიფო სამედიცინო უნივერსიტეტი, უკრაინა

კვლევის მიზანს წარმოადგენდა ვირთაგვების ქვედა ყბისქვეშა სანერწყვე ჯირკვალში მძიმე მეტაბოლური ზემოქმედებით გამოწვეული სტრუქტურული ცვლილებების კორექციის შესაძლებლობის დადგენა პრეპარატ დიალიპონით.

პისტოლოგიურმა კვლევამ გამოავლინა, რომ ვირთაგვებს, რომლებიც დებულობდნენ დიალიპონს, აღენიშნა ჯირკვლოვანი ეპითელიუმის შენარჩუნება, სრტომაში დისტროფიული და დისტირკულაციური ცვლილებების და სკლერო-

ზირების პროცესების უმნიშვნელო გავრცელება, იმ ვირთაგვებთან შედარებით, რომელთაც არ მიეწოდებოდა მაკორექტირებელი პრეპარატი. ასევე, ცხოველთა სხვადასხვა ასაკობრივ ჯგუფში გამოვლინდა კორექტორ დიალიპონის არაერთგვაროვანი ეფექტი, კერძოდ, ახალგაზრდა და ზრდასრულ ვირთაგვებში სტრუქტურული ცვლილებები სრულად აღდგა, ხოლო ასაკოვან ვირთაგვებში გამოვლინდა დაბალი რეპარაციული შესაძლებლობა – სტრუქტურის აღდგენის ხარისხი არასრული და დაბალეფექტურია.

НОВЫЙ МЕХАНИЗМ ГИПОГЛИКЕМИЧЕСКОГО ДЕЙСТВИЯ ЭМБРИОНАЛЬНОГО ПРОТИВООПУХОЛЕВОГО МОДУЛЯТОРА МКРТЧЯНА ПУТЕМ АКТИВАЦИИ ЕГО МЕМБРАНОПРОТЕКТОРНОГО ЭФФЕКТА

Агаджанова Е.М.

Ереванский государственный медицинский университет им. М. Гераци, Армения

Проблема сахарного диабета является одной из основных проблем современной медицины. Несмотря на огромное количество работ, выполняемых в области диабетологии как в эксперименте, так и в клинике, вопрос лечения диабета по сей день не решен. Все существующие методы требуют постоянного введения новых лекарственных препаратов и носят, в основном, симптоматический характер. За последние годы делаются попытки лечения диабета 1 типа путем трансплантации поджелудочной железы или непосредственно островков β -клеток. Однако эти методы далеки от совершенства. Они требуют соответствующий дефицитный материал для трансплантации, довольно сложное хирургическое вмешательство, а также назначение больному пожизненного приема иммунодепрессантов, что создает определенные проблемы для здоровья. На сегодняшний день в научной литературе появилось множество сообщений относительно использования

стволовых клеток в лечении диабета. Однако все эти работы носят экспериментальный характер [28,29,33].

Начавшаяся по всему миру «эпидемия» диабета диктует необходимость проведения мер профилактики на стадии преддиабета на уровне внедрения государственных программ.

Препарат, пригодный для эффективной борьбы с диабетом, должен отвечать следующим требованиям: 1) оказывать регулирующее действие на определенные патогенетические звенья развития диабета и протекторное воздействие на β -клетки поджелудочной железы; 2) обладать длительным эффектом воздействия; 3) терапевтические дозы препарата должны быть лишены способности длительной кумуляции в организме; 4) введение препарата больному должно быть технически не сложным, доступным любому медработнику без специальной