

модельованим обтураційним гепатитом; дослідницька №2 - шури з травмою нижньої щелепи + обтураційний гепатит + комплексний гепатопротектор. В результаті експерименту виявили, що обтураційний гепатит погіршує загоєння кісткової тканини в області післятравматичного дефекту. Застосування гепатопротектора, при експериментальному обтураційному гепатиті, досить ефективно для процесів регенерації кістки в місці перфорації.

Ключові слова: експеримент, шури, травма нижньої щелепи, обтураційний гепатит, гепатопротектор. Стаття надійшла 28.06.2019 р.

челюсти и моделируемым обтурационным гепатитом; экспериментальная №2 - крысы с травмой нижней челюсти + обтурационный гепатит + комплексный гепатопротектор. В результате эксперимента обнаружили, что обтурационный гепатит ухудшает заживление костной ткани в области посттравматического дефекта. Применение гепатопротектора, при экспериментальном обтурационном гепатите, достаточно эффективно для процессов регенерации кости в месте перфорации.

Ключевые слова: эксперимент, крысы, травма нижней челюсти, обтурационный гепатит, гепатопротектор. Рецензент Шепітько В.І.

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V.Ya. Skyba¹, S.S. Polishchuk, I.S. Davydenko², O.I. Shtatko, S.M. Shuvalov, A.O. Gavrilyuk, V.S. Polishchuk, O.O. Polishchuk
National Pirogov Memorial Medical University, Vinnytsya, ¹SI "Institute of Dentistry and Maxillofacial Surgery of the National Academy of Medical Sciences of Ukraine", Odessa
²HSEE of Ukraine "Bukovinian State Medical University", Chernivtsi

DYNAMICS OF MORPHOMETRIC BONE CHANGES IN THE SITE OF MANDIBULAR PERFORATION DEFECT IN RATS WITH TOXIC HEPATITIS AND USE OF HEPATOPROTECTOR

e-mail: polischuk07@ukr.net

The purpose of the work was to experimentally study morphometric changes in the healing of perforation defect of the mandible in rats against the background of toxic hepatitis and the use of complex hepatoprotector. An experimental study was performed on 60 white male Wistar rats weighing 240-270 g. In the experiment process, the rats were divided into 3 groups (20 rats in each group): control - rats with mandibular trauma; group 1 - rats with jaw injury and simulated toxic hepatitis; group 2 - rats with trauma of the mandible + toxic hepatitis + complex hepatoprotector. The study of histological changes in the bone tissue of the mandible in the site of injury, in toxic hepatitis, justified the positive effect of hepatoprotector on changes in morphometric parameters. The experiment results revealed that toxic hepatitis worsened the morphometric parameters of the mandible perforation defect healing. It is particularly important that the complex hepatoprotector in toxic hepatitis increases the specific volume of bone trabeculae on the 30th and the 60th day and bone marrow on the 60th day, which indicates its positive effect on bone regeneration in the site of perforation.

Key words: experiment, rats, mandibular trauma, simulated toxic hepatitis, complex hepatoprotector.

The work is a fragment of the research project "Development of methods for surgical treatment in patients with pathology of the maxillofacial area, taking into account the correction of comorbidities", state registration No. 0118U005403.

Despite the scientific and technological progress and development of mankind in recent years, the number of injuries of the maxillofacial area and their complications still continues to grow [2, 3, 4, 5, 7, 8]. An important place is given to the solution and study of the possible etiopathogenesis of post-traumatic complications. Among the traumatic injuries of the face, the most common are fractures of the lower jaw, nasal bones, zygomaticoorbital complex, upper jaw. Injuries of the maxillofacial area make 15-38% among all examined and hospitalized in the clinic [2, 3, 5, 10, 11]. Maxillofacial fractures among all injuries of the facial skeleton occur in 75-87% of cases according to various authors [2, 3, 5, 6, 8, 11]. In addition, it is known that the share of maxillofacial injuries grows by 3-4% annually, both in our country and abroad. At the same time, about 80% of mandibular fractures occur in men of the most employable age - 20-40 years. This fact explains the urgency of the problem of treating fractures of the facial skeleton and their complications. Fractures of the facial skeleton bones are most frequently of transport and home accident origin [2, 5, 7].

The increase in the total number of injuries also leads to an increase in the frequency of maxillofacial injuries and their complications. All post-traumatic complications of non-gunshot mandible fractures can be divided into early (bone wound suppuration, secondary displacement of fragments, lymphadenitis, abscess, phlegmon, thrombophlebitis of facial veins) and late ones (post-traumatic osteomyelitis, sinusitis, delayed consolidation of fragments, pathological mobility of fragments, malunion, false joint, post-traumatic deformity). Of particular importance is the problem of post-traumatic complications in patients with comorbidities [1, 2, 3, 4, 6, 9], which can have a significant impact on the occurrence and course of post-traumatic inflammatory processes. It should also be remembered that the immediate cause of purulent-inflammatory complications is infection of the area affected by the microflora of the oral cavity and periapical foci of chronic infection. In the injury area there is a sequence of

pathophysiological local and general changes, which subsequently leads to the development of inflammatory processes [2, 3, 5, 8].

Taking into account the above factors, the problem of optimizing osteoreparative processes in fractures of the facial skeleton and prevention of complications should be explained in the context of their association with the presence of concomitant pathology, particularly diseases of the hepatobiliary system. This is primarily due to the high prevalence of liver disease, which occurs in almost 70% of the population [1, 3, 6, 9].

Functions performed by the liver lead to think about its connection with the occurrence of complications in traumatic injuries and inflammatory processes of the maxillofacial area, and in some cases to play one of the key factors. Osteoreparative processes occur due to the properties of a living organism to restore tissue by forming a connective tissue matrix, followed by the process of the fracture site ossification with restoration of the previous tissue structure [2, 3, 4, 5]. At the same time, all efforts of dental surgeons and maxillofacial surgeons should be aimed at improving the regeneration of jaw fractures and faster recovery by preventing development of post-traumatic complications.

In traumatic injuries or inflammatory processes of a maxillofacial site, patients' recovery, first of all, depends on a functional condition of the body which directly depends on the existence of the liver concomitant pathology. It may effect features of the mandible fractures healing, triggering mechanisms that include proliferation and differentiation of cells into osteogenic ones and the synthesis of osteoinductive factors. We have not found information on experimental studies concerning the regeneration of maxillofacial tissues against the background of the liver toxic damage and it needs further study.

The purpose of the work was to experimentally study morphometric changes in the healing of the mandible perforated defect in rats with toxic hepatitis and the use of complex hepatoprotector.

Materials and methods. The experimental study was performed on 60 white male Wistar rats. Rats were on a common diet, had free access to water and food and were kept under the standard living conditions in the vivarium of M.I. Pirogov VNMU. Age of animals was 5-6 months. The weight of rats ranged from 240 to 270 g.

Experimental models of mandibular injuries in laboratory animals have a long history and variety. In a detailed analysis, not all of these techniques can provide objectivity and standardization of the fracture, which, in its turn, will not permit to give an objective assessment of fracture healing and complications [2, 3, 4, 5, 10]. We selected an experimental model of mandibular injury by causing a defect in the area of the rat mandibular angle using a surgical drill with a diameter of 1 mm, which rotated at a speed of up to 10,000 revolutions per minute. The use of this technique permitted to obtain a standard post-traumatic defect of the mandible and to objectively observe the processes of post-traumatic regeneration [2, 3, 5].

In the process of work, the rats were divided into 3 groups:

1. Control - 20 rats - study of morphometric parameters of the mandibular bone tissue in healthy rats in the area of post-traumatic mandible defect.

2. Experimental group 1 - 20 rats - study of morphometric parameters of the mandibular bone tissue in healthy rats in the area of post-traumatic mandibular defect in toxic hepatitis, simulated by the administration of carbon tetrachloride per os.

3. Experimental group 2 - 20 rats - study of morphometric parameters of the mandibular bone tissue in healthy rats in the area of post-traumatic mandibular defect in toxic hepatitis, simulated by the administration of carbon tetrachloride per os, which on the day of the jaw injury and within the following two weeks were added "Quertulin" complex hepatoprotector to their food at a dose of 200 mg per kilogram of rat weight.

"Quertulin" is a complex drug of domestic production containing bioflavonoid quercetin, prebiotic inulin, calcium citrate (permission of the MOH of Ukraine No. 05.03.02. - 06/44464 dated 17.05.2012). Inulin has an antidiabetic effect, stimulating the growth of probiotic microflora, and eliminates the phenomena of dysbiosis. Quercetin has P-vitamin activity, antioxidative, membrane-protective and hepatoprotective action. Calcium citrate is the most easily digestible form of calcium, which stimulates bone tissue mineralization, eliminating the effects of osteoporosis.

In the course of the experimental study, we traced the features of post-traumatic mandibular bone defects regeneration. Quantitative assessment of histological changes was performed using the analysis of morphometric parameters: specific volume (in %) of fibroreticular tissue in the center of bone regeneration, specific volume (%) of blood vessels, specific volume (in %) of bone trabeculae in the center of bone regeneration, the number of osteoblasts in a certain area in the center of bone regeneration, specific volume (%) of bone marrow in the center of bone regeneration. The measurements were performed on the 7th, 14th, 30th, 60th days of the study.

The study was carried out in compliance with the provisions of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (Strasbourg, 1986), Council of Europe Directives 86/609 / EEC (1986), Law of Ukraine №3447-IV "On protection of

animals from cruel treatment”, general ethical principles of animal experiments, approved by the First National Congress of Ukraine on Bioethics (2001).

Numerical values have been statistically processed with calculation of mean values (M) and standard error ($\pm m$). The reliability of discrepancies in the mean values (p) was determined using the Student's t test. Discrepancies were considered reliable at $p < 0.05$.

Results of the study and their discussion. During the experiment on 20 healthy rats of the control group, the features of bone damage regeneration were observed. Quantitative assessment of histological changes was performed using morphometric techniques. From the obtained data presented in table 1, it is noticeable that the specific volume of fibroreticular tissue in the center of bone regeneration on the 7th day is dominant over other elements and makes 91.4%, and on the 60th day it decreases to 12.4%.

Table 1

Morphometric parameters of regenerative tissues at the site of mandibular injury in the dynamics of the experiment in the control group rats (n = 20)

Morphometric parameters	Day of experiment			
	7	14	30	60
specific volume (%) of fibroreticular tissue	91.4 \pm 0.94	56.3 \pm 0.71	48.2 \pm 0.51	12.4 \pm 0.22
specific volume (%) of blood vessels	3.2 \pm 0.05	2.0 \pm 0.05	1.6 \pm 0.05	0.5 \pm 0.01
specific volume (%) of bone trabeculae	1.8 \pm 0.04	12.9 \pm 0.84	48.0 \pm 0.19	72.2 \pm 0.68
Mean number of bone trabeculae osteoblasts in the center of bone regeneration in the area of 100 μm^2	3.5 \pm 0.04	5.7 \pm 0.15	2.0 \pm 0.06	1.0 \pm 0.05
specific volume (%) of bone marrow	0	0	1.6 \pm 0.04	3.8 \pm 0.05

Some single bone trabeculae (1.8%) in this period of the study are explained, of course, not by their new creation, but by the remains of former bone trabeculae, which were at the site of bone injury before the injury. The increased number of osteoblasts per area unit of bone trabeculae (3.5%) should also be noted. Such an increased concentration of them in the bone trabeculae indicates that the old bone trabeculae are also involved in the processes of bone regeneration in the defect site. The specific volume of blood vessels on the 7th day of the experiment in the center of bone regeneration reaches 3.5 percent, and these blood vessels are located almost exclusively in the area of fibroreticular tissue (fig. 1).

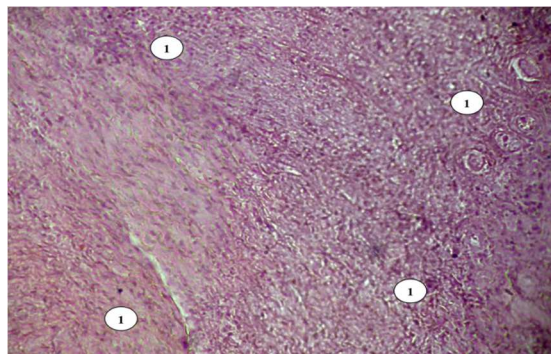


Fig. 1. Bone wound of the rat mandible is replaced by fibroreticular tissue (1), in the site of its perforation on the 7th day of the experiment in the control group. Hematoxylin and eosin. Ob.10x. Oc. 20x.

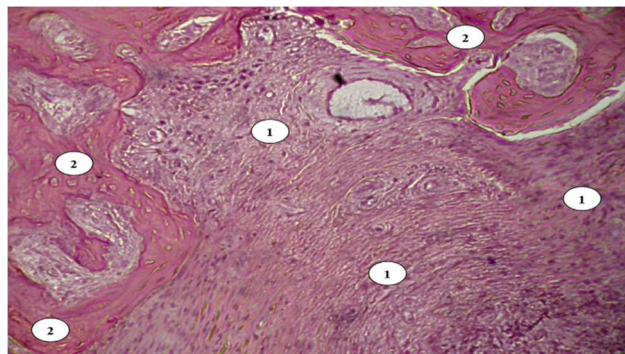


Fig. 2. Bone wound of the rat mandible in the site of its perforation on the 14th day of the experiment in the control group. 1 - fibroreticular tissue. 2 - bone trabeculae. Hematoxylin and eosin. Ob.10x. Oc. 20x.

It should also be noted that on the 7th day there are no formed elements of bone marrow, although in fibroreticular tissue there is a significant presence of cells, which morphologically can be called lymphoid cells, which have a round shape with a round nucleus and a narrow rim of the cytoplasm. It is known that cells with the above morphology can be either lymphocytes or stem (polypotent) cells, of which in the future the elements of the bone marrow are formed. In the dynamics of the experiment in the center of bone regeneration, the specific volume of blood vessels also decreases, and on the 60th day these blood vessels are localized not only in fibroreticular tissue, but also in the bone marrow, which is also manifested on the 30th and moreover on the 60th day.

The specific volume of bone trabeculae up to the 14th day grows more than by 5 times compared to the seventh day (fig. 2), up to the 30th day it still increases (fig. 3) and on the 60th day of the experiment the specific volume of bone trabeculae reaches more than 72 %, i.e. bone trabeculae in this period already make the most part of elements in the zone of bone regeneration (fig. 4).

The mean number of bone trabeculae osteoblasts in the center of bone regeneration in the area of 100 μm^2 decreases at a relatively slow rate. It should be noted that on the 14th day compared the 7th, there is no reliable decrease in the mean number of bone trabeculae osteoblasts in the center of bone regeneration per area unit ($p > 0.05$), except that there is only a tendency to decrease, but on the 30th day compared to the 7th day, the changes, although not pronounced, are still statistically significant ($p < 0.05$).

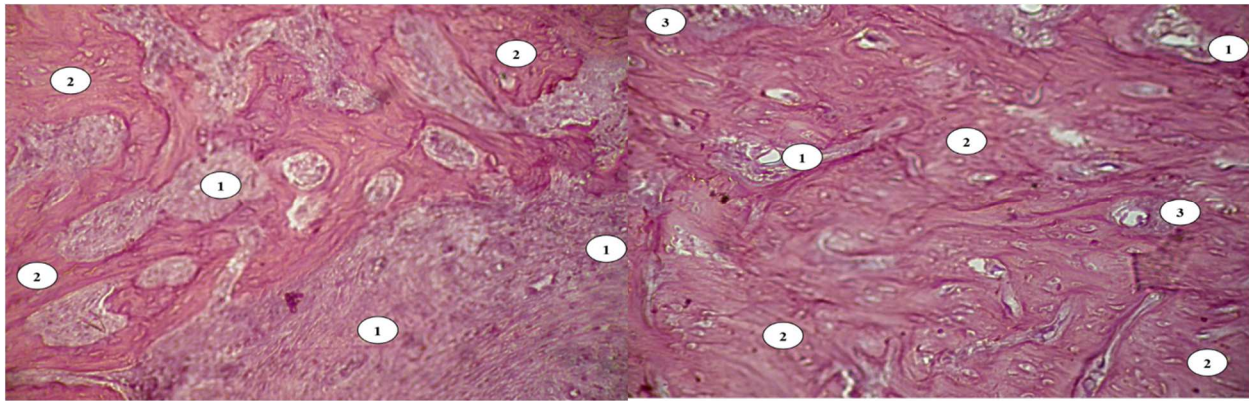


Fig. 3. Bone wound of the rat mandible in the site of its perforation on the 30th day of the experiment in the control group. 1 - fibroreticular tissue. 2 - bone trabeculae. Hematoxylin and eosin. Ob.10x. Oc. 20x.

Fig. 4. Bone wound of the rat mandible in the site of its perforation on the 60th day of the experiment in the control group. 1 - fibroreticular tissue. 2 - bone trabeculae. 3- bone marrow. Hematoxylin and eosin. Ob.10x.Oc. 20x.

The same can be noted for the 60th day of the experiment, when the mean number of bone trabeculae osteoblasts in the center of bone regeneration in the area has the lowest value among all periods of the experiment.

As it has been mentioned above, the obvious elements of the bone marrow are only present in the histological materials of the damaged area in the mandible of rats on the 30th and the 60th day of the experiment. The bone marrow was dominated by hematopoietic elements at different stages of development with a predominance of lymphoid cells, single thin-walled slit-like blood vessels and individual lymphocytes. Thus, a certain sequence of histological changes and a sufficiently high activity of regenerative elements involved in the construction of new bone tissue and replacement of the bone defect were revealed.

The mean data of morphometric parameters of the mandible hard tissues regeneration in the site of injury, in animals of experimental group 1, with toxic hepatitis in the dynamics of the experiment, without drug correction are presented in table 2.

The indices obtained, as it can be seen from table. 2, show a certain dynamics of regenerative processes in the area of mandibular injury, and show the negative impact of toxic experimental hepatitis on the healing processes.

Table 2

Morphometric parameters of the mandibular hard tissues in the site of injury in toxic hepatitis in the dynamics of the experiment without treatment, in rats of experimental group 2 (n = 20)

Morphometric parameters	Days of experiment			
	7	14	30	60
specific volume (%) of fibroreticular tissue	92.0±0.84	88.7±0.76	79.9±0.59	41.0±0.5
specific volume (%) of blood vessels	3.2±0.08	3.0±0.08	2.7±0.04	2.0±0.03
specific volume (%) of bone trabeculae	1.4±0.07	3.8±0.16	11.3±0.12	48.4±0.65
Mean number of bone trabeculae osteoblasts in the center of bone regeneration in the area of 100 μm ²	3.7±0.05	3.6±0.10	3.5±0.07	2.8±0.05
specific volume (%) of bone marrow	0	0	0	1.6±0.02

The changes lie in the fact that in the dynamics of the experiment the specific volume of fibroreticular tissue and blood vessels gradually decreases, the mean number of bone trabeculae osteoblasts in the center of bone regeneration per area unit decreases, but at the same time the specific volume of bone trabeculae increases.

Table 3

Morphometric parameters of the mandibular hard tissues in the site of injury in toxic hepatitis in the dynamics of the experiment under correction with a complex hepatoprotector in rats of experimental group 2 (n = 20)

Morphometric parameters	Days of experiment			
	7	14	30	60
specific volume (%) of fibroreticular tissue	92.6±0.73	73.2±0.74	62.3±0.51	21.9±0.24
specific volume (%) of blood vessels	3.0±0.04	3.0±0.04	3.0±0.05	1.1±0.02
specific volume (%) of bone trabeculae	1.5±0.04	7.5±0.70	28.8±0.14	64.6±0.60
Mean number of bone trabeculae osteoblasts in the center of bone regeneration in the area of 100 μm ²	3.7±0.08	4.8±0.14	2.8±0.06	1.0±0.03
specific volume (%) of bone marrow	0	0	0	2.6±0.04

The proportion of bone trabeculae on the 60th day in animals of experimental group 1 is at the level of the 30th day in rats of the control group, which can indicate deterioration of bone wound healing almost twice. However, in toxic hepatitis, the mean number of bone trabeculae osteoblasts in the center of bone

regeneration per area unit shows the same dynamics. This also applies to the specific volume of bone marrow, which on the 60th day reaches the level of the 30th day in rats of the control group (tables 1, 2).

The experiment with drug correction of regenerative processes in toxic hepatitis by using “Quertulin” in rats of experimental group 2, as shown by morphometric data (table 3), had results that were statistically reliably different in fibrinolytic activity from the results of experimental rats in group 1 [3, 4]. There is a statistically reliable positive effect of complex hepatoprotector on the morphometric parameters of the mandibular regenerative tissues in the defected site [1, 3, 4].

The specific volume of fibroreticular tissue on the 7th day is almost unchanged, but there is a tendency to its sharp reduction on the 14th day. It is particularly important that “Quertulin” in toxic hepatitis increases the proportion of bone trabeculae on the 30th and 60th days and bone marrow on the 60th day [2, 5, 3]. The use of hepatoprotectors in the treatment of patients with fractures of the facial skeleton against the background of the liver toxic damage, will reduce the number of complications and accelerate the recovery of patients [1, 3, 9, 10].

Conclusion

Експериментальне дослідження показало, що токсичний гепатит погіршує морфометричну характеристику загоєння кісткової тканини у ділянці після травматичного дефекту. Використання комплексного гепатопротектора при експериментальному токсичному гепатиті є ефективним заходом для процесів регенерації кістки в місці перфорації, прискорюючи її майже вдвічі. У пацієнтів з травматичними переломом нижньої щелепи, при виявленні патології гепатобіліарної системи, доцільно використовувати «Квертулін», що дозволить скоротити терміни лікування та зменшити кількість ускладнень.

The experimental study showed that toxic hepatitis worsens the morphometric characteristics of bone healing in the area of post-traumatic defect. The use of a complex hepatoprotector in experimental toxic hepatitis is an effective measure for regeneration of bone in the site of perforation, accelerating it almost twice. In patients with traumatic fractures of the mandible, when pathology of the hepatobiliary system is detected, it is advisable to use “Quertulin”, which will reduce the duration of treatment and the number of complications.

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Реферати

ДИНАМІКА МОРФОМЕТРИЧНИХ ЗМІН КІСТКИ У ДІЛЯНКІ ПЕРФОРАЦІЙНОГО ДЕФЕКТУ НИЖНЬОЇ ЩЕЛЕПИ ЩУРІВ ПРИ ТОКСИЧНОМУ ГЕПАТИТІ ТА ВИКОРИСТАННІ КОМПЛЕКСНОГО ГЕПАТОПРОТЕКТОРА
Скиба В.Я., Полищук С.С., Давиденко І.С., Штатко О.І., Шувалов С.М., Гаврилюк А.О., Полищук В.С., Полищук О.О.

Метою дослідження було експериментальне вивчення морфометричних змін при загоєнні перфораційного дефекту нижньої щелепи щурів на фоні

ДИНАМИКА МОРФОМЕТРИЧЕСКИХ ИЗМЕНЕНИЙ КОСТИ В УЧАСТКЕ ПЕРФОРАЦИОННОГО ДЕФЕКТА НИЖНЕЙ ЧЕЛЮСТИ КРЫС ПРИ ТОКСИЧЕСКОМ ГЕПАТИТЕ И ИСПОЛЬЗОВАНИИ КОМПЛЕКСНОГО ГЕПАТОПРОТЕКТОРА
Скиба В.Я., Полищук С.С., Давиденко И.С., Штатко А.И., Шувалов С.М., Гаврилюк А.А., Полищук В.С., Полищук А.А.

Целью исследования было экспериментальное изучение морфометрических изменений при заживлении перфорационного дефекта нижней челюсти крыс на фоне

токсичного гепатиту та використання комплексного гепатопротектора. Було проведено експериментальне дослідження на 60 білих щурах-самцях лінії Вістар масою 240-270 г. В процесі роботи щурі були поділені на 3 групи (по 20 щурів у кожній групі): контрольна – включала здорових щурів з травмою нижньої щелепи; дослідна 1 – щурів з травмою щелепи та модельованим токсичним гепатитом; дослідна 2 – щурів з травмою нижньої щелепи + токсичний гепатит+комплексний гепатопротектор. Дослідження гістологічних змін кісткової тканини нижньої щелепи в ділянці травми, при токсичному гепатиті обґрунтувало позитивний вплив гепатопротектора на зміни морфометричних показників. В результаті експерименту виявили, що токсичний гепатит погіршує морфометричні показники загоєння перфораційного дефекту нижньої щелепи. Особливо важливим є те, що комплексний гепатопротектор при токсичному гепатиті збільшує питомий об'єм кісткових балок на 30 та 60 добу та кісткового мозку на 60 добу, що свідчить про його позитивний вплив на процеси регенерації кістки в місці перфорації.

Ключеві слова: експеримент, щурі, травма нижньої щелепи, модельований токсичний гепатит, комплексний гепатопротектор.

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токсического гепатита и использования комплексного гепатопротектора. Было проведено экспериментальное исследование на 60 белых крысах-самцах линии Вистар массой 240-270 г. В процессе работы крысы были разделены на 3 группы (по 20 крыс в каждой группе): контрольная - включала здоровых крыс с травмой нижней челюсти; экспериментальная № 1 - крыс с травмой челюсти и моделированным токсическим гепатитом; экспериментальная № 2 - крыс с травмой нижней челюсти + токсический гепатит + комплексный гепатопротектор. Исследование гистологических изменений костной ткани нижней челюсти в области травмы при токсическом гепатите обосновало положительное влияние гепатопротектора на изменения морфометрических показателей. В результате эксперимента обнаружили, что токсический гепатит ухудшает морфометрические показатели заживления перфорационного дефекта нижней челюсти. Особенно важно то, что комплексный гепатопротектор при токсическом гепатите увеличивает удельный объем костных балок на 30 и 60 сутки и костного мозга на 60 сутки, что свидетельствует о его положительном влиянии на процессы регенерации кости в месте перфорации.

Ключевые слова: эксперимент, крысы, травма нижней челюсти, моделированный токсический гепатит, комплексной гепатопротектор.

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Ye. V. Stetsuk, O. Ye. Akimov, K. V. Shepitko, A. N. Goltsev¹

Ukrainian Medical Stomatological Academy, Poltava

¹Institute for Problems of Cryobiology and Cryomedicine NAS of Ukraine, Kharkiv

STRUCTURAL ORGANIZATION OF STROMAL AND PARENCHYMAL COMPONENTS OF RAT TESTES DURING CENTRAL DEPRIVATION OF TESTOSTERONE SYNTHESIS ON THE 180 DAY OF THE EXPERIMENT

e-mail: stetsuk78@gmail.com

Prolonged central deprivation of testosterone synthesis may lead to biochemical and morphological changes in testes. Influence of prolonged testosterone deficiency on reactive nitrogen and oxygen species production, morphological changes in interstitial endocrinocytes and sustentocytes is not yet fully understood. The number of interstitial endocrinocytes is reduced in comparison with the control group, there are interstitial spaces between the convoluted tubules with a complete absence of interstitial endocrinocytes. Interstitial endocrinocytes are reduced in size, their nuclei are heterochromic. When we studied the structural organization of rat sustentocytes from the experimental group in comparison with the control group, we found that hyperplasia of the elements of the smooth endoplasmic reticulum was observed in the cytoplasm of the sustentocytes. The number of mitochondria in the cytoplasm of the sustentocytes decreased, the electron density of the mitochondrial matrix was lowered, protein structures were present either inside the vacuoles or independently located in the cell cytoplasm. Biochemical studies revealed increased NO production from inducible NO-synthase and development of oxidative stress. Experimental central deprivation of testosterone synthesis with diphereline on the 180th day of the experiment leads to shift of NO synthesis from constitutive NO-synthases to inducible NO-synthase and intensification of oxidative stress due to increase of superoxide anion-radical production and decrease in antioxidant protection.

Key words: testes, interstitial endocrinocytes, sustentocytes, NO-synthase, iNOS, cNOS, L-arginine, superoxide dismutase, rats.

The study is a fragment of the research project "Experimental morphological study of cryopreserved placenta transplants: action of diphereline, ethanol and 1% methacrylic acid on the morphofunctional status in a number of internal organs", state registration No. 0119U102925.

In developed European countries, there is a trend towards high sexual activity in older men and the late creation of a family with children, which has certain difficulties in connection with a decrease in testosterone production in old age [2, 10]. At the same time uncontrolled usage of testosterone leads to increase of prostate cancer incidence since androgens play key role in its development [4].

Diphereline is a potent treatment method for prostate cancer treatment, however we showed in our previous works that its usage leads to development of oxidative stress and changes in sustentocytes and interstitial endocrinocytes [3, 7, 14]. Minimal duration of diphereline intake in prostate cancer treatment