Научно-практический журнал
ФАРМАЦИЯ И ФАРМАКОЛОГИЯ

ОРИГИНАЛЬНАЯ СТАТЬЯ

DOI: 10.19163/2307-9266-2019-7-6-321-331

STRUCTURAL TRANSFORMATIONS OF THERMAL BURN WOUNDS IN RATS UNDER THE INFLUENCE OF SEMAX AND SELANK NEUROPEPTIDES

A.K. Azhikova[1], B.V. Feldman[1], L.A. Andreeva[2], D.D. Teply[3], M.A. Samotrueva[1], N. F. Myasoedov[2]

[1] Astrakhan State Medical University
121, Bakinskaya Str., Astrakhan, Russia 414000
[2] Institute of Molecular Genetics, Russian Academy of Sciences
2, Acad. Kurchatov Square, Moscow, Russia 123182
[3] Astrakhan State University
1, Shahumyan Square, Astrakhan, Russia 414000

E-mail: alfia-imacheva@mail.ru

Received 8 August 2019 Review (1) 25 October 2019 Review (2) 18 November 2019 Accepted 11 December 2019

The morphological features of the skin of rats under the stress exposure, such as burn injury and against the background of the correction by the drugs of the peptide structure, have been studied.
The aim of the study was to investigate the regulatory effect of the neuropeptide drugs Semax (Met-Glu-His-Phe-Pro-Gly-Pro) and Selank (Thr-Lys-Pro-Arg-Pro-Gly-Pro) under the conditions of thermal burn exposure.
Materials and methods. The object of the study was integumentary tissues (skin, subcutaneous tissue) of laboratory non-linear male rats (n = 36) excised from the thermal injury zone. A thermal burn of the skin had been caused by the application of a copper object in the interscapular in the interscapular dorsal area. Starting from the first day after the injury, neuropeptide drugs Semax (Met-Glu-His-Phe-Pro-Gly-Pro) and Selank (Thr-Lys-Pro-Arg-Pro-Gly-Pro) had been administered intraperitoneally at the doses of 100 μg/kg daily during the entire period of the experiment. To assess the condition of the skin tissues, histological sections 5–6 μm thick were preparев, stained afterwards with hematoxylin and eosin. The consistency of the systemic effect of the neuropeptide drugs was estimated by a change in some indicators of the immune system.
Results. The thermal exposure led to the development of significant degenerative and dystrophic changes in the skin. The recovery of the burn wounds on rats' skins proceeded according to the type of the delayed partial reparative regeneration, accompanied by destructive phenomena and the formation of the scar tissue.
Under the influence of the drugs based on the regulatory peptides of Semax (Met-Glu-His-Phe-Pro-Gly-Pro) and Selank (Thr-Lys-Pro-Arg-Pro-Gly-Pro), the recovery of burn wounds in rats proceeded more intensively, compared with the animals from the group without any correction. This fact was confirmed by the earlier signs of the beginning of the reparative skin regeneration: the restriction of destructive processes within the epidermis and dermis, the absence of purulent-necrotic complications, the initial phases of granulation and epithelization, an early scab rejection and a partial closure of the defect.
Conclusion. The use of the neuropeptide drugs Semax and Selank as systemic remedies for the correction of wound skin defects in experimental animals proves their polypotent effectiveness, expands the therapeutic possibilities and opens up new prospects for their use.
Keywords: burn wound, structural transformations, neuropeptide regulation, Semax, Selank

СТРУКТУРНЫЕ ПРЕОБРАЗОВАНИЯ ТЕРМИЧЕСКОЙ ОЖОГОВОЙ РАНЫ У КРЫС В УСЛОВИЯХ ВОЗДЕЙСТВИЯ НЕЙРОПЕПТИДОВ СЕМАКС И СЕЛАНК

А.К. Ажикова[1], Б.В. Фельдман[1], Л.А. Андреева[2], Д.Д. Теплый[3], М.А. Самотруева[1], Н.Ф. Мясоедов[2]

[1] Федеральное государственное бюджетное образовательное учреждение высшего образования «Астраханский государственный медицинский университет» Министерства здравоохранения Российской Федерации
414000, Россия, г. Астрахань, ул. Бакинская, д. 121
[2] Федеральное государственное бюджетное учреждение науки Институт молекулярной генетики Российской академии наук
123182, Россия, г. Москва, пл. акад. Курчатова, 2

For citation: A.K. Azhikova, B.V. Feldman, L.A. Andreeva, D.D. Teply, M.A. Samotrueva, N.F. Myasoedov. Structural transformations of thermal burn wounds in rats under the influence of Semax and Selank neuropeptides. *Pharmacy & Pharmacology*. 2019;7(6): 321-331. **DOI:** 10.19163/2307-9266-2019-7-6-321-331

Для цитирования: А.К. Ажикова, Б.В. Фельдман, Л.А. Андреева, Д.Д. Теплый, М.А. Самотруева, Н.Ф. Мясоедов. Структурные преобразования термической ожоговой раны у крыс в условиях воздействия нейропептидов Семакс и Селанк. *Фармация и фармакология.* 2019;7(6): 321-331. **DOI:** 10.19163/2307-9266-2019-7-6-321-331

RESEARCH ARTICLE

ISSN 2307-9266 e-ISSN 2413-2241

Scientific and Practical Journal
PHARMACY & PHARMACOLOGY

[3] Федеральное государственное бюджетное образовательное учреждение высшего образования
Астраханский государственный университет
414000, Россия, г. Астрахань, пл. Шаумяна, 1

E-mail: alfia-imacheva@mail.ru

Получено 08.08.2019 Рецензия (1) 25.10.2019 Рецензия (2) 18.11.2019 Принята к печати 11.12.2019

В работе изучены морфологические особенности кожи крыс при стрессорном воздействии – ожоговой травме и на фоне коррекции лекарственными средствами пептидной структуры.

Цель исследования – изучение регулирующего влияния нейропептидных лекарственных средств Семакса (Met-Glu-His-Phe-Pro-Gly-Pro) и Селанка (Thr-Lys-Pro-Arg-Pro-Gly-Pro) в условиях термического ожогового воздействия.

Материалы и методы. Объектом исследования служили покровные ткани (кожа, подкожная клетчатка) лабораторных животных-нелинейных крыс-самцов (n=36), иссеченные из зоны термической травмы. Термический ожог кожи вызывали наложением медного предмета в межлопаточной области спины крыс. Начиная с первых суток после травмы внутрибрюшинно вводили нейропептидные лекарственные средства Семакс (Met-Glu-His-Phe-Pro-Gly-Pro) и Селанк (Thr-Lys-Pro-Arg-Pro-Gly-Pro) в дозах 100 мкг/кг ежедневно в течение всего периода эксперимента. Для оценки состояния тканей кожи изготавливали гистологические срезы толщиной 5–6 мкм, которые окрашивали гематоксилином и эозином. Состоятельность системного влияния нейропептидных препаратов оценивали по изменению некоторых показателей иммунной системы.

Результаты. Термическое воздействие вело к развитию значительных дегенеративных и дистрофических изменений в коже. Восстановление ожоговой раны кожи крыс протекало по типу замедленной частичной репаративной регенерации, сопровождающейся деструктивными явлениями и формированием рубцовой ткани. Под влиянием лекарственных средств на основе регуляторных пептидов Семакса (Met-Glu-His-Phe-Pro-Gly-Pro) и Селанка (Thr-Lys-Pro-Arg-Pro-Gly-Pro) восстановление ожоговых ран у крыс протекало интенсивнее, по сравнению с животными из группы без коррекции, что подтверждалось более ранними признаками начала репаративной регенерации кожи: ограничением деструктивных процессов в пределах эпидермиса и дермы, отсутствием гнойно-некротических осложнений, начальными фазами грануляции и эпителизации, ранним отторжением струпа и частичным закрытием дефекта.

Заключение. Применение нейропептидных лекарственных средств Семакса и Селанка в качестве системных средств коррекции раневых дефектов кожи экспериментальных животных доказывает их полипотентную эффективность, расширяет терапевтические возможности и раскрывает новые перспективы их применения.

Ключевые слова: ожоговая рана, структурные преобразования, нейропептидная регуляция, Семакс, Селанк

INTRODUCTION

In recent years, the study of pathogenesis of thermal skin injuries has been aimed at identifying the peculiarities of the response of immune, nervous and endocrine systems which provide mechanisms for activating regenerative processes. This study has also been aimed at searching for new means of correcting intersystem interactions in pathological changes [1–4]. Numerous studies consider complex relationships through which reactions of neurogenic and immunologically induced inflammation, are carried out under the conditions of skin damage [5–8].

Against the background of thermal stressful effects, alongside with destructive, dystrophic [9–13] and infectious manifestations in the skins, Imbalance, dysfunction of immunocompetent cells, insufficient local resistance [14–17], disorganization in the emotional zones of the brain [17–20], formation and triggering of stress-adaptive and / or stress-maladaptive reactions take place [22–26]. Currently, peptide drugs that act as regulators of the intersystem interaction, are actively used as effective remedies for the correction of stress-induced disorders of homeostasis in the clinical practice. In this regard, neuropeptide drugs with a nootropic, neurometabolic, immunomodulating effect, in particular, an adrenocorticotropic hormone analogue, Semax (Met-Glu-His-Phe-Pro-Gly-Pro) and a Tuftsin derivative, Selank (Thr-Lys- Pro-Arg-Pro-Gly-Pro), are of great interest [27, 28]. The use of synthesized peptide preparations increases the adaptive abilities of the body under stressful conditions, helps restore the structures of the central nervous system, and corrects immune and humoral disorders. In addition, under the stress exposure, these drugs have a corrective effect on somatic disorders, restoring adequate motivational activity and activating adaptive behavior [27–29]. Experimental and clinical data also confirm anxiolytic, antidepressant, psychoactivating, stress-protective, vegetotropic effects of these drugs [32–34]. However, the results of recent studies do not give a complete picture of the reparative potential of these drugs and the mechanisms of their stimulating dermatropic action.

Nowadays, the stimulation of the skin's regenerative potential is reduced to the use of the agents that comprehensively correct violations of neuroimmune endocrine interactions and the skin [35, 36]. One of the types of the systemic treatment is a neuropeptide correction. So, in the study on the immunotropic, antioxidant effects of a new thymogen analog H2N-L-Glu-L-Trp-D-Ala-COOH, modified with the D-alanine from the C-terminus of the peptide under the conditions of skin wounds, the reparative properties of the neuropeptide have also been established [37].

An experimental study of the peptide preparations Gly-His-Lys, dalargin and thymogen, revealed their participation in the reparative regeneration of the skin, ex-

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2019-7-6-321-331

pressed by the activation of reparative processes and stimulation of healing skin wounds [38]. A significant improvement in the course of psoriasis treatment has been proven: a decrease in the activity of the inflammatory process and a decrease in the area of psoriasis-affected skin in the patients taking Semax as a part of the complex therapy.

The results of the study describing a combined treatment of acne with the Semax neuropeptide drug and a supravenous laser blood irradiation, showed a decrease in skin manifestations and a change in personality self-esteem among alexithymic patients [39]. The use of Semax in the complex treatment of acne patients, contributed to an increase in the clinical efficacy of the therapy.

An important role of regulatory peptides in the correction of physiological stress-limiting mechanisms, is evidenced by the Semax correction as a part of the complex therapy of atopic dermatitis [40]. It has been found out that the use of heptapeptide has a beneficial effect on the reduction of itching, sleep quality and dynamics of the dermatological indices against the background of the absence of the side effects characteristic of a glucocorticoid hormone therapy.

The obtained results substantiate the position of a close structural and functional specific interaction of the neuroendocrine, immune systems and skin, both under physiological conditions and in the development of certain skin pathologies.

The research data on the detection of the healing neuropeptides effects, have determined the scientific interest and significance of studying the neuropeptide regulation of reparation under the conditions of burn exposure.

THE AIM of the study was to investigate the regulatory effect of the neuropeptide drugs Semax (Met-Glu-His-Phe-Pro-Gly-Pro) and Selank (Thr-Lys-Pro-Arg-Pro-Gly-Pro) under the conditions of thermal burn exposure.

MATERIALS AND METHODS

Laboratory research

The experiment was carried out on 36 non-linear white male rats, aged 7 months, weighing 200–230 g, provided by the Federal State Budget Educational Institution of Higher Education "Astrakhan State University" (Astrakhan). The animals were kept under standard vivarium conditions (natural light conditions, at the air temperature of 22–24°C and the humidity of 60±5%) at the Department of Pharmacognosy, Pharmaceutical Technology and Biotechnology (FSBEI HE Astrakhan State Medical University, Ministry of Health of Russia), in individual cages with a sawdust litter and a free access to water and food.

The animals were divided into 4 groups depending on the type of the exposure and correction:

Group I – the animals not exposed to burn effects – intact (n = 8);

Group II – the animals exposed to burn effects and not receiving correction remedies (control, n = 8);

Group III – the animals exposed to burn effects and receiving a daily intraperitoneal administration of 100 mg/kg Semax peptide dissolved in water (n = 10);

Group IV – the animals exposed to burn effects and receiving a daily intraperitoneal administration of Selank peptide dissolved in water at the dose of 100 μg/kg (n = 10).

During the experiment, the general condition of the laboratory animals was estimated. All manipulations with animals 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, 1986), the Helsinki Declaration adopted by the General Assembly of the World Medical Association (1964–2013), Order No. 199n of the Ministry of Health of Russia dated April 1 2016 "On the approval of the rules of good laboratory practice".

Burn injury model

The burn wounds on the rats' skins, were modeled in the depilated zone of the interscapular dorsal area with the help of a copper object with the diameter of 1.5 cm, heated in boiling water to the temperature of 100° C, under the conditions of weak ether anesthesia. The exposure duration was 5 seconds.

In the animals of the control group, the reparation of the skin defect took place naturally. Starting from the first day after the thermal exposure, the individuals of experimental groups III and IV were administrated intraperitoneally with Semax and Selank peptides dissolved in water, respectively (Peptogen Innovation Research and Production Center, Russian Federation, Institute of Molecular Genetics, Russian Academy of Sciences, Russia), at the dose of 100 mcg/kg a day for 10 days daily, throughout the whole period of the experiment.

During the experiment, the general condition of the animals was observed [41], the appearance and size of the burn wounds, the nature of the discharge and the timing of the scab discharge were evaluated, photographings surveys of the wound surfaces were carried out.

The complex effect of neuropeptide drugs was estimated by a change in some indicators of the immune system. The functional activity and adaptability of the immune system were estimated by the following tests – determining the total number of leukocytes, assessing the leukocyte formula and leukocyte coefficient, and determining the mass of immunocompetent organs.

The degree of reparation of the skin defect was estimated planimetrically. To do this, a transparent film coating was applied to the wound with the borders of the wound marked. The size and area of the wounds were measured immediately after the simulation of burn wounds and then daily till the end of the experiment. During the experiment, the wound surface was determined according to the method developed by V.Ya. Vasyukov, N.V. Protsenko (1993). The area of the wound surface corresponded to the area of the circle: $S = \pi \times R^2$, where R is the distance from the center of the wound to its periphery.

Based on the parameter of "the wound area", the percentage reduction of the wound area from the initial size was calculated, which served as a criterion for the rate of epithelization of the damaged skin. The degree of healing of a burn wound, or the rate of epithelialization (ΔS), was calculated as a percentage of a change in the area relative to the original group, according to L.N. Popova' formula (1942): $\Delta S = ((S - Sn)/S \times t) \times 100$, where: S is the size of the wound area in the first measurement (cm^2), Sn is the value of the area of the wound on the day of the subsequent measurement (cm^2), t is the number of the days between measurements.

Sampling and preparation of biomaterial

Skin tissues were a biological material in the study. The material was sampled on the 10th day after the start of the experiment. The animals were taken out of the experiment under anesthesia by decapitation using sodium etaminal. For the morphological study of the skin, the tissues (epidermis, dermis, subcutaneous tissue) excised from the zone of the thermal damage in the interscapular dorsal area of the rats of all studied groups, were used.

The skin samples were fixed in 10% neutral buffered formalin (Biovitrum LLC, Russia). The material was washed, carried out on solutions of alcohols of various concentrations, solutions of xylene, then it was embedded in paraffin, and sections 5–6 μm thick were made. To assess the general morphological state of the skin layers, they were stained with hematoxylin and eosin.

Microscopic observations of histological preparations were carried out in transmitted light at 100x magnification (10x lens, WF-10x/18 eyepiece) of the Altami BIO 8 digital biological trinocular microscope (Altami LLC, Russia). Microphotography was carried out using a 3 megapixel camera and Altami Studio 3.4x64/Ink software.

Methods of statistical processing of results

Statistical processing of the results was carried out using the Excel 2000 program by methods of variation statistics, including the calculation of average values (M), standard errors of average values (± m). To assess the reliability (significance) of differences between the two average values, Student t-test with Bonferroni correction was used. The differences were considered significant at $p \leq 0.05$.

RESULTS

As a result of the experimental study it was established that a thermal burn on the skin of the rats caused not only local reactions, but also led to changes in the general condition of the body – there was "fading" and loss of hair, disorganized movements of the animals along the cage and a decrease in the dynamics of weight gain.

A microscopic analysis of histological skin tissue sections of the rats' burn wounds of all experimental groups, showed the presence of structural changes in the skin compared with the intact animals (group I – control) (Fig. 1). The epidermis of the interscapular area of the intact rats is represented by stratified squamous keratinizing epithelium. The stratum corneum is represented by a uniform layer. In the prickly layer, there are up to 2 rows of keratinocytes, in the granular layer there are 2–3 rows of nuclear-free cells. At the level of the germinal or malpighian layer, epithelial cells are visible. The cells of the basement membrane are arranged in a single row. On the level of the dermis, there are sebaceous glands and hair follicles, vessels of the microvasculature.

Along with the signs of the general behavioral disorganization, in the animals of the second group, pronounced destructive changes capturing the epidermis, dermis and hypodermis were observed. In this case, inflammation phenomena prevailed over reparative ones. In the area of the burn surface, a purulent inflammatory reaction was observed macroscopically, in some animals a hemorrhagic scab of a gray-brown color was observed. By the 10th day, there was a sucrose discharge in the animals, the wound cavity was covered with a necrotic mass.

It was microscopically revealed that the heat affected zone was devoid of stratified squamous epithelium, and in some places, necrotic elements in the form of folds were observed. The hyperemic dermis looked edematous due to the serous inflammation, a large amount of exudate and cellular elements; there was no pronounced differentiation into papillary and reticular layers. The papillary layer of the epidermis was disrupted. In the reticular layer, intercellular swelling and infiltration by macrophages and lymphocytes were observed. The basal membrane could not be clearly determined (Fig. 2).

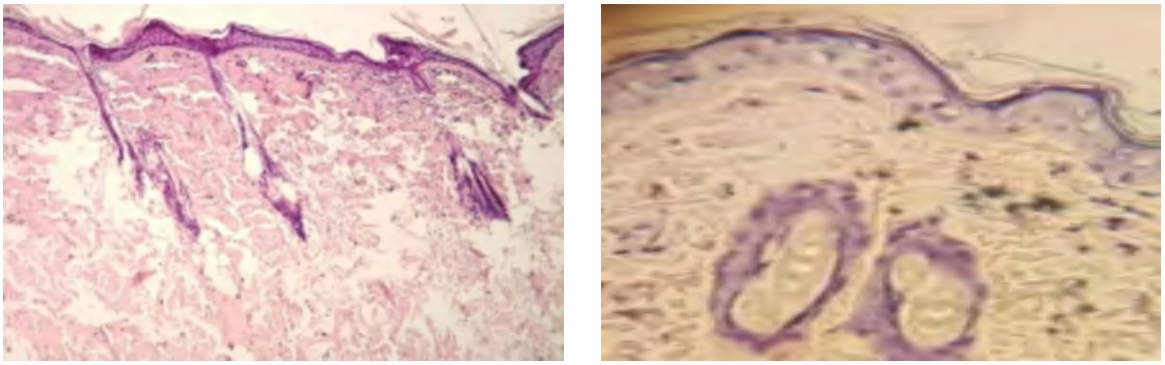
Against the background of the thermal injury correction of the rats' skins with preparations of a neuropeptide nature, the animals of groups III and IV showed signs of improvement in the general condition, activity restoration and positive weight dynamics.

One of the stages of the work was the study of the rats' immune state in conditions of a "burn" stress and its correction.

As a result of the research of Semax and Selank effect on the total number of leukocytes and leukocyte counts under thermal burn conditions, it was established that these peptide preparations activated the leukocyte reaction: the total number of leukocytes increased; among them lymphocytes, eosinophils, monocytes, segmented neutrophils were restored to normal values.

The administration of neuropeptides led to a decrease in stab forms of neutrophils by more than 50% ($p<0.001$), to a normalization of the number of segmented neutrophils by 50% ($p<0.001$). (Tab. 1). An increase in the level of the Garkavi index under the conditions of thermal burns, can be interpreted as the degree of the response to the stress state, the so-called "reactivation" of the body in the conditions of an active inflammatory process. The use of Semax and Selank contributed to the restoration of the index to normal values, and the activation of adaptation reactions.

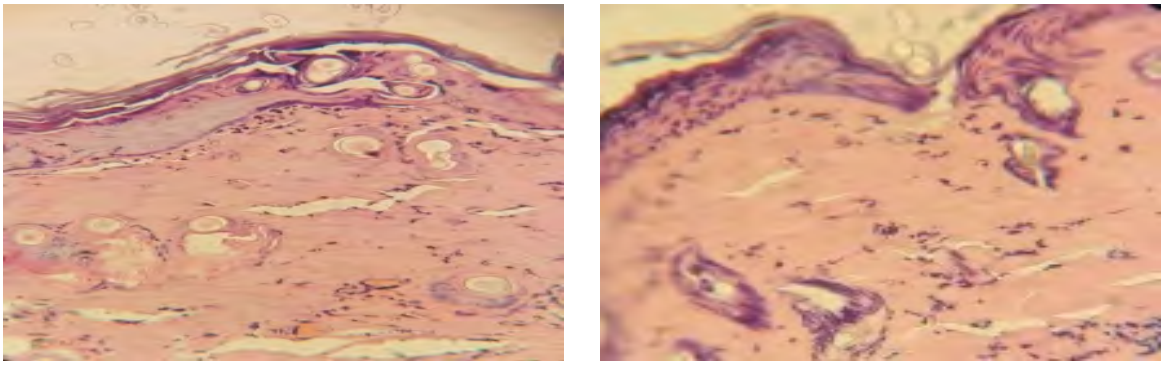
ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2019-7-6-321-331



A B

Figure 1 – Micrograph of a skin flap excised in intact rats on day 10

Note: stained with hematoxylin and eosin (UV. X100, vol. 10x (A). UV. X 400, vol. 40x (B), approx. WF-10x / 18)



A B

Figure 2 – Micrograph of a skin flap excised in the wound 10 days after the burn exposure in the rats not treated with correction remedies

Note: stained with hematoxylin and eosin (UV. X100, vol. 10x (A). UV. X 400, vol. 40x (B), approx. WF-10x / 18)

A – The edge of the burn wound. At the level of the epidermis and dermis, there is a pronounced coagulation necrosis and inflammatory infiltration; in the underlying fatty tissue there is lymphoid infiltration (hyperplasia of lymphoid follicles).

B – Necrotic changes in violation of the structure of tissues

Table 1 – The effect of Semax and Selank neuropeptides on the functional activity of the immune system

Experimental groups (n = 10) / Indices (M ± m)	Group I Intact Group	Group II Control Group	Group III (animals treated with Semax)	Group IV (animals treated with Selank)
Total number of leukocytes, x109/l	27.7±0.4	84.5±4.5*	103.3±0.2###	99.3±0.6##
Eosinophils, %	5.7±0.2	4.3±0.2***	6.7±0.2###	6.3±0.2###
Stab neutrophils, %	12.0±0.4	26.5±0.6*	14.2±0.2###	14.9±0.4###
Segmentonuclear neutrophils, %	19.3±0.2	13.9±0.4***	20.8±0.2###	19.7±0.4###
Lymphocytes, %	61±0.6	53.7±1.1*	56.3±0.4##	57.3±0.6#
Monocytes, %	2.0±0.2	1.6±0.2*	2.0±0.1##	1.8±0.2##
Leukocytal coefficient	3.1±0.4	3.9±0.4*	2.7±0.2##	2.9±0.4##
Thymus mass, mg	51±0.4	31±5.4**	73±6.0##	68±0.4##
Spleen mass, mg	352.3±0.6	456±10.3**	572±39.6##	583±31.4##

Note: * – p <0.05; ** – p <0.01; *** – p <0.001 – relative to the intact group; # – p <0.05; ## –p <0.01; ### – p <0.001 - relative to the control group; Student t-test with Bonferroni correction for multiple comparisons.

The study has also established that thermal burns provoked involution of immunocompetent organs: the spleen – by more than 60% ($p < 0.01$), the thymus – by more than 40% ($p < 0.01$). The studied drugs contributed to an increase in the mass of the spleen by an average of 40% ($p < 0.01$), as well as the mass of the thymus by more than 50% ($p < 0.01$), compared with the control group.

In the course of macroscopic observations it was found out, that the use of Semax and Selank neuropeptides at the dose of 100 μg/kg a day under the conditions of thermal burn exposure leveled the development of the inflammatory process, helped to tighten the edges of the wound and, as a result, reduce its size on the 4th day. As the data in Tables 2 and 3 show, a decrease in the area of the burn wound by more than 60% ($p < 0.01$) in the experimental groups on the 10th day of the post-burn process was observed. It corresponded to the acceleration of wound recovery by 30% ($p < 0.05$), compared with the control group (Tab. 4, 5).

In Group III of the animals exposed to burn effects and treated with Semax, the wound surface was weakly edematous in the center, and along its edges there were growing hair shafts. There were inflammatory manifestations of the surrounding tissues in the form of a mild swelling. The boundaries of the wound narrowed significantly. Under a partially detached scab, an increase in granulation tissue was manifested. From the edges of the wound, there was also an epithelium growth.

A microscopic analysis of the skin fragments excised on the 10th day of the experiment in the area of the thermal injury, showed slightly destroyed epidermal layers and a partial necrosis of the stratified squamous epithelium. The epidermis was represented by a dark plate, sometimes exfoliated from the papillary dermis. Under the scab, the regenerate zone was determined in the form of a wide layer of newly formed granulation tissue (Fig. 3).

The papillary layer looked edematous, without contours of connective tissue fibers, but dark nuclei of connective tissue cells were identified. The papillary layer retained uneven edges. The reticular layer appeared to be broad, mildly swolen; dark nuclei of connective tissue cells were observed. The lower part of the mesh layer was infiltrated by lymphocytes. Hair follicles made of necrotically altered collagen fibers, were found out; single cells with light nuclei were found in hair sheaths. Mild neoangiogenesis was observed.

A macroscopic analysis of burn animal the IV groups wounds showed that on the 10th day after the burn exposure and Semax correction, a slightly swollen and hyperemic wound with uneven outlines, without purulent exudate and necrotic elements, was observed on the rats' skin. The inflammation of the tissue surrounding the wound, was moderate. The process of the peripheral wound epithelization was visualized. There was an increase in granulation tissue from the bottom of the wound. Under a partially detached scab, skin appendages appeared.

A morphological picture in the area of the burn wound of the skin excised on the 10th day after the burn exposure and Selank correction (Group IV) (Fig. 4), is comparable with the visualization of Semax activity. During this time period, activation of vascular neoplasm, hypertrophy of the border zone of the epidermis were established, and proliferating cells were noticeable. The upper layers of the epidermis were exfoliated. In their place, dark layers were found out. They had exfoliated from the basement membrane. The basal membrane itself was represented by a wide dark-colored plate on the papillary layer. The papillary layer was characterized by a small width and a wavy shape. In the upper part of it, there was a partial necrosis. The reticular layer was wide, its upper part was saturated with the nuclei of connective tissue cells. Necrotic changes were observed in the lower part of the reticular layer, although lymphocyte infiltration occurred in most fields of view. Hair follicles consisting of necrotic altered collagen fibers, were established. In the lower parts of the hair sheaths, separate epithelial light cells with rounded nuclei were determined. Around the hair follicles, lymphocyte infiltration was notified.

DISCUSSION

The problem of post-burn skin regeneration is of great medical and social importance due to the significant prevalence of burn injuries, the complexity of the pathogenesis of burn injuries, disability, features of social disadaptation, and a high mortality rate [42]. The causes of mortality are microvascular and membrane lesions, burn sepsis, metabolic and hormonal changes, profound systemic disorders and the development of multiple organ failure syndrome [33]. Despite the experience gained in the treatment of burn diseases, the matter of morphogenetic changes during the thermal injury to the skin, remains poorly studied and determines the relevance of the problem.

During the experimental study it was established that under the conditions of the thermal injury to the skin during the first three days, not only local skin inflammatory reactions but also a change in the general condition of the body are observed: "fading" and hair loss, disorganized movement of animals along the cage, lethargy, lack of dynamism, a decrease in the dynamics of weight gain. Based on the results of a morphological study of fixed skin tissues, significant degenerative changes in the damaged skin and inhibition of reparative processes have been revealed. Recovery of a burn wound of the skin in the animals of the control group proceeded physiologically, accompanied by destructive phenomena and the formation of scar tissue.

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2019-7-6-321-331

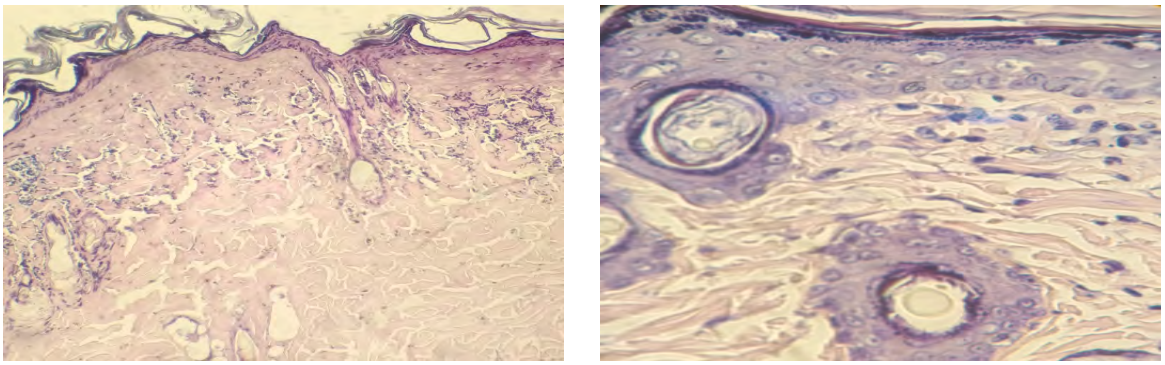
Table 2 – Dynamics of changes in the areas of burn wounds in rats under conditions of thermal injury to the skin and against the background of exposure to Semax and Selank

Group	№	Observation time (days)/Wound square area, cm2				
		1	3	5	7	10
Control group	1	1.76	1.76	1.63	1.50	1.42
	2	1.76	1.76	1.63	1.51	1.41
	3	1.76	1.76	1.62	1.54	1.39
	4	1.76	1.75	1.62	1.52	1.42
	5	1.76	1.75	1.62	1.57	1.39
	6	1.76	1.76	1.63	1.52	1.41
	7	1.76	1.76	1.63	1.54	1.42
	8	1.76	1.75	1.61	1.53	1.34
Group III (animals treated with Semax)	1	1.76	1.54	1.34	1.14	0.78
	2	1.76	1.58	1.37	1.19	0.74
	3	1.76	1.55	1.35	1.18	0.77
	4	1.76	1.53	1.32	1.19	0.79
	5	1.76	1.57	1.34	1.13	0.76
	6	1.76	1.58	1.35	1.18	0.69
	7	1.76	1.58	1.39	1.19	0.78
	8	1.76	1.59	1.35	1.17	0.77
	9	1.76	1.59	1.36	1.18	0.78
	10	1.76	1.55	1.31	1.16	0.77
Group IV (animals treated with Selank)	1	1.76	1.59	1.33	1.19	0.74
	2	1.76	1.58	1.32	1.22	0.80
	3	1.76	1.59	1.31	1.24	0.77
	4	1.76	1.53	1.34	1.28	0.79
	5	1.76	1.58	1.33	1.24	0.77
	6	1.76	1.58	1.33	1.29	0.78
	7	1.76	1.58	1.32	1.25	0.79
	8	1.76	1.59	1.35	1.27	0.81
	9	1.76	1.57	1.28	1.24	0.79
	10	1.76	1.57	1.33	1.29	0.81

Table 3 – Planimetric indicators of the wound surface in rats under conditions of thermal injury to the skin and against the background of exposure to Semax and Selank

Groups of animals	Wound square area, cm^2				
	Day	Day 3	Day 5	Day 7	Day 10
Group II (Control)	1.76	1.76±0.01	1.62±0.01	1.53±0.01	1.4±0.01
Group III (animals treated with Semax)	1.76	1.56±0.01***	1.35±0.01***	1.17±0.01***	0.76±0.01*
Group IV (animals treated with Selank)	1.76	1.58±0.01***	1.32±0.01***	1.25±0.01***	0.79±0.01*

Note: * – p <0.05; ** – p <0.01; *** – p <0.001 – relative to the control group (Student t-test with Bonferroni correction for multiple comparisons).



A **B**

Figure 3 – Micrograph of a skin flap excised in the wound area on day 10 after the burn exposure in rats treated with Semax

Note: stained with hematoxylin and eosin (UV. X100, vol. 10x (A). UV. X 400, vol. 40x (B), approx. WF-10x / 18); A – Mild swelling of the tissues. Moderate leukocyte infiltration in the underlying fibrous and adipose tissue. B – Full-blood vessels and moderate leukocyte infiltration (individual sections of leukocyte diapedesis through the capillary wall into the tissue)

ISSN 2307-9266 e-ISSN 2413-2241

Scientific and Practical Journal
PHARMACY & PHARMACOLOGY

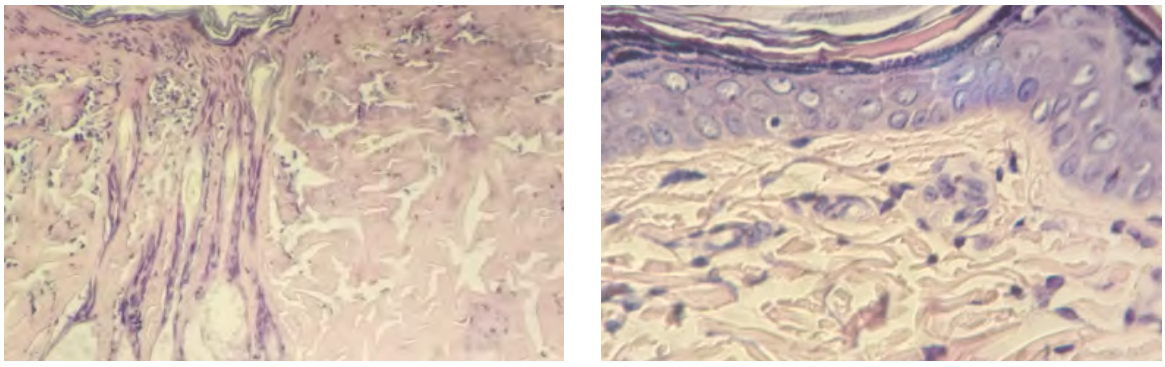
Table 4 – Dynamics of burn wounds recovery in rats under conditions of thermal injury to the skin and against the background of exposure to Semax and Selank

Group	№	Observation time (days)/ Recovery rate (%)				
		1	3	5	7	10
Control group	1	0.00	0.00	7.39	14.77	19.32
	2	0.00	0.00	7.38	14.20	19.89
	3	0.00	0.00	7.95	12.50	21.02
	4	0.00	0.56	7.95	13.64	19.32
	5	0.00	0.56	7.95	10.79	21.02
	6	0.00	0.00	7.39	13.64	19.89
	7	0.00	0.00	7.39	12.50	19.32
	8	0.00	0.56	8.52	13.07	23.86
Group III (animals treated with Semax)	1	0.00	12.5	23.9	35.2	55.7
	2	0.00	10.2	22.2	32.4	57.9
	3	0.00	11.9	23.3	32.9	56.3
	4	0.00	13.1	25.0	32.4	55.1
	5	0.00	10.8	23.9	35.8	56.8
	6	0.00	10.2	23.3	32.9	60.8
	7	0.00	10.2	21.0	32.4	55.7
	8	0.00	9.7	23.3	33.5	56.3
	9	0.00	9.7	22.7	32.9	55.7
	10	0.00	11.9	25.6	34.1	56.3
Group IV (animals treated with Selank)	1	0.00	9.7	24.4	32.4	57.9
	2	0.00	10.2	25.0	30.7	54.5
	3	0.00	09.7	25.6	29.5	56.3
	4	0.00	13.1	23.9	27.3	55.1
	5	0.00	10.2	24.4	29.5	56.3
	6	0.00	10.2	24.4	26.7	55.7
	7	0.00	10.2	25.0	28.9	55.1
	8	0.00	9.7	23.3	27.8	54.1
	9	0.00	10.8	27.3	29.5	55.1
	10	0.00	10.8	24.4	26.7	54.1

Table 5 – Epithelization rate of burn wounds in rats under conditions of thermal injury to the skin and against the background of exposure to Semax and Selank (M ± m)

Groups of animals	Epithelization rate (%)				
	1 Day	Day 3	Day 5	Day 7	Day 10
Group II (Control)	0.00	0.21±0.24	7.74±0.35	13.14±1.04	20.46±1.31
Group III (animals. treated with Semax)	0.00	11.02±0.41***	23.42±0.55*	33.45±0.40**	56.66±0.68*
Group IV (animals treated with Selank)	0.00	10.46±0.44***	24.77±0.48*	28.9±0.68**	55.42±0.45*

Note: * – p <0.05; ** – p <0.01; *** – p <0.001 – relative to the control group (Student's t test with Bonferroni correction for multiple comparisons).



A B

Figure 4 – Micrograph of a skin flap excised in the wound area on day 10 after burn exposure in rats treated with Selank

Note: stained with hematoxylin-eosin (UV. X100, vol. 10x (A). UV. X 400, vol. 40x (B), approx. WF-10x / 18)

A – A fragment of the skin with underlying tissues. In the underlying tissues, there is a moderate diffuse leukocyte infiltration.

B – A fragment of skin with underlying tissues. At the level of the dermis, there is swelling; in the underlying fibrous tissue, there are foci of a moderate leukocyte infiltration reaching the dermis

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2019-7-6-321-331

At present, the search and development of effective means of correcting skin lesions, as well as determining the role of pathogenetic links of complex systemic homeostasis disorders of the body, are of great interest in reparating skin wounds of various origins, stimulating tissue reparation. Taking into account a close relationship between the skin, immune, nervous and endocrine systems, in the study of the pathogenesis of skin wounds and its regenerative potential, special attention is paid to studying the regulation of these processes by the neuroimmunoendocrine interactions and their disorders.

Today, regulatory peptides are increasingly being used as effective remedies for correcting homeostasis disorders under the conditions of stress, in particular, the adrenocorticotropic hormone analogue Semax (Met-Glu-His-Phe-Pro-Gly-Pro) and a tuftsin derivative Selank (Thr-Lys-Pro-Arg-Pro-Gly-Pro). The use of synthesized peptide preparations increases the adaptive capabilities of the body under stressful conditions, helps restore the structures of the central nervous system, and corrects immune and humoral disorders.

However, the results of recent studies do not give a complete picture of the reparative potential of these drugs and the mechanisms of their stimulating dermatropic action.

The carried out study on the assessment of morphological characteristics of the rats' skins under the conditions of thermal injury to the skin in the animals treated with Semax and Selank, established mild degenerative and dystrophic changes in the burn wounds by stimulating start adaptive reparative processes in the skin and a systemic regulation of reparations.

A microscopic analysis of the structural features of the skin layers in the rats treated with neuropeptide preparations Semax and Selank intraperitoneally, confirmed the earlier onset of skin regenerative regeneration processes. That phenomenon manifested itself in the decrease of the destructive phenomena in the wound and leveling of inflammatory reactions, as well as the signs of early scab exfoliation, the formation of granulation tissue and accelerated epithelization of burn wounds. In the course of studying the systemic effect of Semax and Selank under the conditions of thermal exposure, it has been found out that these neuropeptide preparations have regulatory, stress-adaptive and immunocorrection properties. They reparate the leukocyte formula, leukocyte coefficient and weight of immunocompetent organs (the thymus and spleen). Such positive results prove the viability of systemic coordination in stimulating the regenerative potential of damaged skin and other pathological processes in the body.

CONCLUSION

Up-to-date understanding of the molecular mechanisms of the complex regulation of the skin pathophysiological processes, Is at the heart of the systemic approach in. It proves their polypotent effectiveness, expands the therapeutic possibilities and opens up new prospects for their application.

The results of the experimental study make it possible to suggest the following qualities of neuropeptide drugs Semax and Selank: they contributes to the regulation and stimulation of reparative processes, which gives grounds to consider them as correction remedies for skin wounds with local and systemic effects, realized through neuroimmune endocrine mechanisms. The above determines the importance and necessity of the next stages of research in this direction.

The above analysis determines the importance and necessity of the next stages of research in this direction.

FINANCIAL SUPPORT AND SPONSORSHIP

This study did not have any financial support from outside organizations.

AUTHOR'S CONTRIBUTION

All authors equally contributed to the research work.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Abdulloev DA, Holov B., Chakalov TG, Zubajdov TU. Vlijanie reamberina v sochetanii v meksidolom na pokazateli gomeostaza u bol'nyh s termicheskoj travmoj [influence of «Reamberin» in combination with «Mexidol» on homeostasis of patients with thermal injury]. Avicenna's messenger. 2013; 4(3):32–5. (in Russ)
2. Doncova EV. Immunnye narushenija u bol'nyh psoriazom s metabolicheskim sindromom i ih korrekcija pri kompleksnoj terapii s ispol'zovaniem medikamentoznyh i nemedikamentoznyh sredstv [Immune violations at patients with psoriasis with a metabolic syndrome and their correction at complex therapy with use of medicamentous and non-drug means]. Kursk scientific and practical bulletin Person and its health]. 2014; 1:65–8. Russian
3. Kolter J, Feuerstein R, Zeis P, Hagemeyer N, Paterson N, d'Errico P, Baasch S,Amann L, Masuda T, Lösslein A, Gharun K, Meyer-Luehmann M, Waskow C, Franzke CW, Grün D, Lämmermann T, Prinz M, Henneke P. A Subset of Skin Macrophages Contributes to the Surveillance and Regeneration of Local Nerves. Immunity. 2019 Jun 18; 50(6):1482-97.e7. DOI: 10.1016/j.immuni.2019.05.009.
4. Zhou S, Hokugo A, McClendon M, Zhang Z, Bakshi R, Wang L, Segovia LA, Rezzadeh K, Stupp SI, Jarrahy R. Bioactive peptide amphiphile nanofiber gels enhance burn wound healing. Burns. 2019 Aug;45(5):1112–21. DOI: 10.1016/j.burns.2018.06.008.
5. Vukolova MN, Kurochkina IM. Patofiziologicheskij analiz ranevogo processa i zazhivlenija ran [The pathophysiological analysis of wound process and healing of wounds]. In the collection: Youth in science: new arguments collection of scientific works of the V International youth competition. 2016:138–43. Russian
6. Fistal EYa. Ranevoj process i rezul'taty hirurgicheskogo lechenija obshirnyh ran – vzgljad na problem [Wound process and results of early surgical treatment of extensive wounds] The Messenger of urgent and recovery surgery. 2016; 1(2): 157–63. Russian.
7. Stepenko YV, Soldatov VO, Zatolokina MA, Mayorova AV, Sysuev BB, Demidenko AN, Ivahno EN, Sarycheva MV, Pokrovskiy MV.

Stimulation of reparation in a linear wound model in rats by bischofit gel. Pharmacy & Pharmacology. 2019;7(1):42–2. DOI: https://doi.org/10.19163/2307-9266-2019-7-1-42-52

8. Aleksandrova AV. Stimuljacija zazhivlenija ozhogovoj rany sinteticheskim ingibitorom matrichnyh metalloproteinaz doksiciklinom [Stimulation of healing of a burn wound synthetic inhibitor of matrix metalproteinases doxycycline]. Collection of theses conf. young scientists and students «Topical issues of diagnostics and treatment of pain». Harkiv. 2011: 6–6. Russian
9. Kirichenko AK, Bol'shakov IN, Ali-Riza AE, Vlasov AA. Morfologicheskiy analiz zazhivleniya ozhogovoy rany pri primenenii kollagen-khitozanovogo ranevogo pokrytiya [The morphological analysis of healing of a burn wound at application collagen hitozanovy wound pokrittya]. The Bulletin of experimental biology and medicine. 2012; 154(1): 652–6. Russian
10. Glutkin AV, Koval'chuk VI, Ostrovskaya OB. Morfologicheskie izmeneniya kozhi pri termicheskom ozhoge u krysyat v usloviyakh korrektsii vnutrivennym lazernym oblucheniem krovi i emoksipinom [Morphological changes of skin at a thermal burn in infant rats in the conditions of correction by intravenous laser radiation of blood and emoksipiny]. Journal of Grodno State Medical University. 2013; 3(43): 87–91. Russian
11. Shestakova VG, Bazhenov DV. Korellyatsiya protsessov angiogeneza i epitelizatsii pri reparativnoy regeneratsii posloynoy khirurgicheskoy rany kozhi [Correlation of processes of angiogenesis and an epitelization at reparative regeneration of a layer-by-layer surgical wound of skin]. Current problems of morphology, adaptogenez and reparative gistogenez: materials of the international scientific conference devoted to memory of the corresponding member of the USSR Academy of Medical Sciences, professor F.M. Lazarenko. Ed.A.A. Stadnikov, etc. Orenburg. 2013: 44–5. Russian
12. Khuskadamov ZK, Mirsoev HM. Sudebno-meditsinskaya otsenka ozhogovoy travmy ot goryuchikh zhidkostey po morfologicheskim izmeneniyam vnutrennikh organov [The justice madicine of marching of the burning trauma from the burning by a morphological chaugrbility in internal argons]. News of Academy a spider of the Republic of Tajikistan. 2009; 3:99–102. Russian
13. Voronkov AV, D'yakova IN, Ogurtsov YuA, Zhidkova YuYu, Gamzeleva OYu. Study of the influence of Original Multicomponent Gels on the Process of Pathological Scar Formation Using New Methodological Approach. Experimental and Clinical Pharmacology. 2014; 77(9):38–42. (in Russ)
14. Bulankina IA. Izmeneniya morfologicheskikh kharakteristik i biomekhanicheskikh svoystv struktur kozhi pri termicheskom ozhoge kozhi I, II stepeni [Changes of morphological characteristics and biomechanical properties of structures of the leather at thermal burn I, II degree]. Siberian medical journal (Irkutsk). 2012; 112(5): 78–80. Russian
15. Telesheva LF, Osikov MV, Likhacheva AG. Pokazateli vrozhdennogo immuniteta i morfologiya ochaga povrezhdeniya pri eksperimental'noy termicheskoy travme [Indicators of congenital immunity and morphology of the center of damage at an experimental thermal trauma]. Fundamental researches. 2012; 8(2): 381–386. Russian
16. Liu SS, Ge HY, Cheng SL, Zou Y, Zhang KL, Chu CX, Gu NL. Synthesis of Graphene Oxide Modified Magnetic Chitosan Having Skin-Like Morphology for Methylene Blue Adsorption. J Nanosci Nanotechnol. 2019; Dec 1;19(12):7993–8003. DOI: 10.1166/jnn.2019.16872.
17. Bakhach J, Abou Ghanem O, Bakhach D, Zgheib E. Early free flap reconstruction of blast injuries with thermal component. Ann Burns Fire Disasters. 2017; Dec 31;30(4):303–308. PubMed PMID: 29983687; PubMed Central PMCID: PMC6033485.
18. Kaddoura I, Abu-Sittah G, Ibrahim A, Karamanoukian R, Papazian N. Burn injury: review of pathophysiology and therapeutic modalities in major burns. Ann Burns Fire Disasters. 2017 Jun 30;30(2): 95–102. PubMed PMID: 29021720; PubMed Central PMCID: PMC5627559.
19. Maden M. Optimal skin regeneration after full thickness thermal burn injury in the spiny mouse, Acomys cahirinus. Burns. 2018 Sep;44(6): 1509–1520. DOI: 10.1016/j.burns.2018.05.018.
20. Mathias E, Srinivas Murthy M. Pediatric Thermal Burns and Treatment: A Review of Progress and Future Prospects. Medicines (Basel). 2017 Dec 11;4(4). pii: E91. DOI: 10.3390/medicines4040091.
21. Pielesz A, Biniaś D, Bobiński R, Sarna E, Paluch J, Waksmańska W. The role of topically applied l-ascorbic acid in ex-vivo examination of burn-injured human skin. Spectrochim Acta A Mol Biomol Spectrosc. 2017 Oct 5;185: 279–285. DOI: 10.1016/j.saa.2017.05.055.
22. Makieva MS, Morozov YuA, Voronkov AV, Stepanova EF, Remezova IP, Pozdnyakov DI. Development of transdermal gel with Schizandra and the assessment of the extent of its effect on working capacity and neurologic status of animals in experiment. Medical News of the North Caucasus. 2016; 1194):532–6. DOI: 10.14300/mnnc.2016.11126 (in Russ)
23. Abdullahi A, Amini-Nik S, Jeschke MG. Animal models in burn research. Cell Mol Life Sci. 2014 Sep;71(17): 3241–3255. DOI: 10.1007/s00018-014-1612-5.
24. Abraham JP, Stark J, Gorman J, Sparrow E, Minkowycz WJ. Tissue burns due to contact between a skin surface and highly conducting metallic media in the presence of inter-tissue boiling. Burns. 2019 Mar; 45(2):369–378. DOI: 10.1016/j.burns.2018.09.010.
25. Pogorielov M, Kalinkevich O, Gortinskaya E, Moskalenko R, Tkachenko Y. The experimental application of chitosan membrane for treating chemical burns of the skin. Georgian Med News. 2014 Jan;(226):65–70. Russian. PubMed PMID: 24523336.
26. Jurjus A, Hourani R, Daouk H, Youssef L, Bou-Khalil P, Haidar H, Atiyeh B, Saade N. Effect of denervation on burn wound healing. Ann Burns Fire Disasters. 2018 Dec 31; 31(4): 278–291. PubMed PMID: 30983928; PubMed Central PMCID: PMC6441573.
27. Slominsky PA, Shadrina MI, Kolomin TA, Filatova EV, Andreeva LA, Myasoedov NF, Stavrovskaya AV, Illarioshkin SN. Peptidy Semaks i Selank vliyayut na povedenie krys v usloviyakh eksperimental'noy modeli bolezni Parkinsona [Peptides Semaks and Selank affect behavior of rats in the conditions of experimental model of Parkinson's disease]. Doklady Akademii nauk [Doklady Biological Sciences.]. 2017; 474 (2): 264–267. Russian
28. Tereshchenko ON, Kost NV, Medvedev VE, Myasoyedov NF. Kupirovanie trevozhnykh rasstroystv v obshchemeditsinskoy praktike peptidnym preparatom Selank [Therapy of anxiety disorders in general practice by peptide preparation selank]. Archive of internal medicine. 2016; 6(51):115–116. Russian
29. Kalistratov VB, Dehkhanov TG, Plotnikova OV. Otechestvennye nejropeptidy Selank i Semaks v sovremennoj psihofarmakoterapii [Domestic neuropeptids Selank and Semaks in modern psychopharmacotherapy]. In the collection: Intense violations of brain blood circulation. Questions of diagnostics, treatment, rehabilitation Materials of an interregional scientific and practical conference. 2018: 47–8. Russian
30. Verbenko VA, Shakina TA. Osobennosti anksioliticheskogo i stressoprotektivnogo deystviya peptidnogo preparata Selank® pri terapii rasstroystv adaptatsii i posttravmaticheskogo stressovogo rasstroystva // [Features of anxiolytic and stressoprotektivny effect of the peptide medicine Selank® at therapy of disorders of adaptation and post-traumatic stressful frustration]. Meditsinskiy alfavit [The Medical alphabet]. 2017; 3 (32): 21–6. Russian
31. Golubeva MG. Neyropeptid Semaks izmenyaet funktsional'nuyu aktivnost' eritrotsitov i trombotsitov pri immobilizatsionnom stresse. [Neuropeptide Semax changes erythrocites and platelets functional activity under immobilization stress]. Thrombosis, hemostasis and rheology. 2010; 2 (42): 45–9. Russian
32. Lalayan T, Korzhavlna N. Selank v lechenii bolevogo sindroma v poyasnichno-kresttsovom otdele pozvonochnika [The influence of selank on course of pain syndrom in patients with chronic pain syndroms of lumbosacral spine]. Doctor. 2014; 9: 30–4. Russian
33. Spiridonova TG, Smirnov CB, Borovkova NV, Lazareva EB, Bitkova EE, Hvatov VB. Korrektsiya sistemnogo vospalitel'nogo otveta dlya profilaktiki poliorgannoy nedostatochnosti u obozhzhennykh [Correction of systemic inflammatory response for prevention of multi-organ insufficiency in burned patients]. Emergency medical service. 2006. 7(3): 88–9. Russian

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2019-7-6-321-331

34. Skrebitsky VG, Kasyan AP, Povarov IS, Kondratenko RV, Slominsky PA. Neyropeptidnyy preparat Selank: biologicheskaya aktivnost' i fundamental'nye mekhanizmy deystviya [Biological Activity and Basic Mechanisms of Action of Selang – a Neuropeptide Product]. Nervous diseases. 2016. 4:52–7. Russian
35. Kosareva IN, Silina LV, Pismennaya EV, Provotorov VY. Otsenka vliyaniya preparata Semaks na effektivnost' antioksidantnoy zashchity u bol'nykh psoriazom [Assessment of the administration of Semax in antioxidant therapy of patients with psoriasis]. Scientific statements of the Belgorod State University. Series: Medicine. Pharmacy. 2012; 22-1(141): 83–6. Russian
36. Sapuntsova SG, Lebed'ko OA, Obuchova GG, Berezina GP, Timoshin SS. Vliyanie geptapeptida Semaks na soderzhanie faktora nekroza opukholey-al'fa i biogenez svobodnykh radikalov pri atopicheskom dermatite [Effect of heptapeptide semax on the level of tumor necrosis factor-alpha and biogenesis of free radicals in patients with atopic dermatitis]. Far East Medical Journal. 2015;2:61–4. Russian
37. Smakhtin MYu, Bobyncev YaI, Koroshvili VT, Chulanova AA, Dolzhikova IN. Immunotropnye, antioksidantnye i reparativnye effekty novogo analoga timogena, modifitsirovannogo D-alaninom [Immunotropic, antioxidant and reparative effects of a new thymogen analogue modified with D-alanine]. Kursk scientific and practical bulletin Person and its health. 2019; 1:77–82. DOI: 10.21626/vestnik/2019-1/09. Russian
38. Cherdakov VYu, Smakhtin MYu, Dubrovin GM, Bobyntsev II. Sinergichnoe immunotropnoe i reparativnoe deystvie timogena, dalargina i regulyatornogo peptida Gly-His-Lys pri eksperimental'noy travme kozhi [The sinergic immunothropic and reparative action of Thymogen, Dalargin and regulatory peptide glycyl-histidyl-lysine in experimental skin trauma]. Kursk scientific and practical bulletin Person and its health. 2013; 1:38–42. Russian
39. Zheltysheva AS. Novye terapevticheskie podkhody k lecheniyu akne [New therapeutic approaches to treatment of acne]. Journal of New Medical Technologies. 2011;18 (2): 384–6. Russian
40. Pereverzeva IV, Bobyntsev II, Silina LV. Klinicheskaya effektivnost' kompleksnoy terapii atopicheskogo dermatita s primeneniem Semaksa [Clinical effectiveness of complex therapy of atopic dermatitis with Semax]. Kursk scientific and practical bulletin Person and its health. 2008; 2: 98–103. Russian
41. Spasov AA, Bugaeva LI, Lebedev SA, Korzhova TM, Getmanenko AY. Vliyanie alimentarnoy gipomagneziemii na obshchee sostoyanie laktiruyushchikh krys-samok i postnatal''noe sostoyanie ikh potomstva [The influence of alimentary hypomagnesaemia on the general condition of lactating female rats and postnatal status of their offspring]. Journal of Volgograd State Medical University. 2017. 3(63):113–7. DOI: 10.19163/1994-9480-2017-3(63)-113-117 Russian
42. Alekseev AA, Tyurnikov YuI. Osnovnye statisticheskie pokazateli raboty ozhogovykh statsionarov Rossiyskoy Federatsii za 2015 god [Main statistical indicators of burn hospitals in the Russian Federation for 2015]. Combustiology. 2016: 56–7. Russian

AUTHORS

Alfiya K. Azhikova – Candidate of Sciences (Biology), Assistant Professor of the Department of Biology and Botany, Federal State Budgetary Educational Institution of Higher Education "Astrakhan State Medical University", the Ministry of Health of the Russian Federation. ORCID: 0000-0001-9758-1638. E-mail: alfia-imacheva@mail.ru

Bronislav V. Feldman – Doctor of Sciences (Biology), Associate Professor, the Head of the Department of Biology and Botany, Federal State Budgetary Educational Institution of Higher Education "Astrakhan State Medical University", the Ministry of Health of the Russian Federation. ORCID: 0000-0001-7205-986X. E-mail: agmafarm@gmail.com

Lyudmila A. Andreeva – the head of the regulatory peptides sector of the Department of Chemistry of Physiologically Active Substances, Federal State Budgetary Institution of Science Institute of Molecular Genetics of the Russian Academy of Sciences. ORCID: 0000-0002-3927-8590. E-mail: landr@img.ras.ru

Dmitry D. Teply – Candidate of Sciences (Biology), Senior Researcher at the Joint Laboratory for the Study of the Role of Apoptosis in the Formation of the Neuroendocrine System, Federal State Budgetary Educational Institution of Higher Education "Astrakhan State Medical University", the Ministry of Health of the Russian Federation. ORCID: 0000-0002-3484-9710. E-mail: dima.tepliy@yandex.ru

Marina A. Samotrueva – Doctor of Sciences (Medicine), the Head of the Department of Pharmacognosy, Pharmaceutical Technology and Biotechnology, Federal State Budgetary Educational Institution of Higher Education "Astrakhan State Medical University", the Ministry of Health of the Russian Federation. ORCID: 0000-0001-5336-4455. E-mail: ms1506@mail.ru

Nikolay F. Myasoedov – Doctor of Sciences (Chemistry), Professor, Academician of the Russian Academy of Sciences, the Head of the Department of Chemistry of Physiologically Active Substances, Federal State Budgetary Institution of Science "Institute of Molecular Genetics of the Russian Academy of Sciences". ORCID: 0000-0003-1294-102X. E-mail: nfm@img.ras.ru