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ПОКАЗАТЕЛИ СОСТОЯНИЯ ИММУННОЙ И АНТИОКСИДАНТНОЙ СИСТЕМ В КРОВИ БЕРЕМЕННЫХ САМОК КРЫС F_1 ВСЛЕДСТВИЕ ДЕЙСТВИЯ РАЗЛИЧНЫХ ДОЗ ЦИТРАТА ГЕРМАНИЯ

Исследовано и изучено влияние различных доз цитрата Ge, полученного методами нанотехнологии и химического синтеза, на активность иммунной и антиоксидантной систем крови беременных самок крыс. Исследования выполнены на самках крыс F_1, которым выпаивали с водой цитрат Ge в дозах 10 (II), 20 (III), 200 (IV) мкг Ge, полученный нанотехнологическим методом, и 2000 (V) мкг Ge – химически синтезированным. Цитрат Ge применяли от молочного периода до 18-20 суток беременности. Отмечено разнонаправленное влияние цитрата Ge на показатели иммунной и антиоксидантной систем с повышением содержания иммунных глобулинов, гликопротеинов и активности энзимов антиоксидантной защиты, что более выражено у самок, которые получали 20 мкг Ge. Установлено ингибирующее влияние цитрата Ge в дозе 2 мг/кг на содержание альбумина и триацилглицеролов на фоне повышения уровня креатинина в крови беременных самок.

Ключевые слова: цитрат германия; кровь; крысы; иммунофизиология.

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THE INDICATORS OF THE IMMUNE SYSTEM AND ANTIOXIDANT IN THE BLOOD OF PREGNANT FEMALE RATS F1 BY ACTION OF DIFFERENT DOSES OF GERMANIUM CITRATE

The aim of research was to study the effect of different doses of Ge citrate, obtained by nanotechnology method and chemically synthesized, the activity of their immune and antioxidant system blood of pregnant female rats. Research performed on rats F_1 which were watering Ge citrate obtained by nanotechnology method in doses 10 (II), 20 (III), 200 (IV) mcg Ge and chemically synthesized Ge citrate in dose 2,000 (V) mg Ge. Ge citrate watering during the milk-feeding period up to 18-20 days of pregnancy. Not the same directional effect Ge citrate parameters of immune and antioxidant systems with increased content of immune globulin, glycoproteins and activity of enzymes of antioxidant protection that is more pronounced in females receiving 20 mcg Ge. Established inhibitory effect of Ge citrate 2 mg/kg albumin content and threeacylglycerol, amid increasing the level of creatinine in the blood of pregnant females V group which may indicate a decrease of albumin-transport function of filtering and absorption the ability of the kidneys.

Key words: germanium citrate; blood; rat;, immunophysiology.

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CORRECTION OF MELANIN PROTEOLYTIC ACTIVITY IN THE CONDITIONS OF MODELING ALKALI BURNS OF THE ESOPHAGUS

During the esophageal burns first and second degree, were observed the increase of total proteolytic activity and of the main proteinase (metalloproteinases and serine). Experimental melanin correction at a dose of 0.1 mg / kg contributed to the normalization of the pathological increase of total proteolytic activity and the activity of the main proteinase (metalloproteinases and serine), which indicates the normalization of the proteolysis system.

Keywords: alkaline burn of the esophagus, proteolysis, melanin.

Esophageal burns takes the first place among all diseases of the esophagus with severe pathological condition, accompanied by profound and often irreversible local general changes in the body. Chemical burns the esophagus remains one of the major problems of clinical medicine. [1,2,3]. Medical statistics show that among the total number of people who received burns of the esophagus, 70.0 % are children under the age of 10 years. Often the cause of impaired patency of esophageal stricture is a scar that is caused by chemical burns [2,3, 4]. Tissue damages due the breach cell membranes as a result of the dissolution of lipids that make up their basic structural unit. Necrosis is observed not only in mucosa – the process can spread to the entire thickness of the submucosal and muscle layers. For chemical burns of the esophagus, regardless of the severity of lesions are three major successive processes: alternative-destructive, reparative and restorative without the appearance or the appearance of preconditions to chronic inflammation. Burn wound in most cases prone to chronic due to prolonged inflammation and high proteolytic activity [5].

According to modern concepts proteolisis is considered as a special form of biological control, which occupies a leading place in realization of variety biochemical processes and rapid physiological response of the body to unstable conditions of endogenous and exogenous environment. Proteinase, active participants of the proteolysis system, perform a huge variety of functions and control practically all levels of biological processes occurring at the molecular, cellular, tissue and organ levels [6]. Regulatory role of proteolytic enzymes is carried in two forms: full and limited proteolysis. Full proteolysis is the degradation of protein cleavage abnormal and damaged proteins. At the same time limited proteolysis is considered a universal mechanism responsible for the creation, modification and inactivation of hormones, enzymes and other physiologically active substances. In some pathological conditions occur excessive activation of proteolysis, which is an important link in the pathogenesis of destructive, inflammatory, allergic reactions, disturbance of hemostasis, as well as one of the factors that contributes to cell invasion of tumors [7]. The reaction of proteolysis has a key role not only in the regulation of intracellular protein metabolism, but also in processes such as their translocation inside and outside the cell, the formation of active enzymes, hormones and other biologically active substances [8].

Integral role in balancing of the physiological synthesis and proteolysis play inhibitors proteinases [9]. These

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specific proteins prevent excessive destruction of protein compounds, allowing timely or slow down, or stop any biological process. Violation of proteinase-inhibitory system can be both a cause and a consequence of pathological conditions. However, excessive activation of proteolysis causes damage of native tissue proteins, promotes activation of inflammatory processes, the flow of which is the rapid destruction of the ECM and cell migration [10].

Despite the large number of drugs used for this purpose in the literature is conflicting information about their effectiveness and sufficiently acute is the problem of shortening the healing of burn wounds, prevent post burns complications [11,12,13]. Actual is the use of non-toxic natural antioxidants as cytoprotectors [14]. The protective effect of antioxidants is widely studied under the influence of adverse factors, metabolic disorders. With deep burns of the esophagus, it is important to provide assistance quickly because any delay or improper treatment can significantly slow down the healing process or cause serious infection. Today, the market has a lot of drugs for the treatment of burns, still lacks ideal preparation, as most of the available products have only antimicrobial activity but does not affect on the process of wound healing. In addition, these products can be toxic for intact cells and cause allergic reactions. [15] Medicinal plants rich in phenolic compounds could potentially accelerate healing process in burn wounds and protects the wound from bacterial infections [16]. An additional advantage of using herbal medicines rich in polyphenols in the treatment of burns is their low cost, high availability, and fewer side effects [16]. In burns there is a violation of homeostasis between reactive oxygen species and antioxidant defense systems in the body [17]. Antioxidant activity of phenolic compounds occurs through different mechanisms of action: inhibition of the formation of reactive oxygen species, the ability to neutralize singlet oxygen molecule, to bind metal ions that are catalysts of reactions, leading to the formation of reactive oxygen species, interrupting the cascade of reactions of free radicals in the lipids peroxidation [18,19,20,21]. Analysis of recent literature suggests that possible promising remedy in normalization of proteinase-inhibition imbalance during esophageal burns first and second degree can be substances of natural origin based on polyphenolic compounds. To these substances belongs melanin, which is the waste products of yeast fungi Nadsoniella nigra strain X-1 [22]. This product demonstrates antioxidant [23,24,25], immunomodulatory [26, 27], anticarcinogenic [26, 28] and stress-protective [29] properties, which allows its use in medicine. Melanin also has a pronounced cytoprotective effect on the gastric mucosa of rats, reducing the activity of lipid peroxidation and increases the activity of antioxidant enzyme system [30].

Therefore, the aim of this study was to determine the total proteolytic activity and activity of the main proteinase (metalloproteinases and serine) in rats with esophageal burns first and second degree on the background of the drug in melanin dose of 0.1 mg / kg.

Materials and methods. White wild rats (1-month, 90-110 g body weight) were used in experiments in compliance with provisions for the use of animals in biomedical experiments approved by the First Ukrainian National Congress on Bioethics (September 2001) and other international agreements and national legislation in this area. Chemical burns in animals were experimentally modeled in the following way: alkaline esophageal burn was caused by 10 % and 20 % NaOH and acid esophageal burn was caused by, for this injected the probe into the esophagus soldered up end and a hole at a distance of 2 mm from it. The probe was injected to a depth of 4 cm from the upper incisors rat and slowly injected 0.1 solution of 10 % NaOH, modeling changes corresponding to the 1st degree burn injury. Similarly injected 0.2 ml of 20 % NaOH, thereby reproducing the 2 degree burns. The control rats once orally administered the appropriate amount of water for injection [1, 31]. Studied animals received a standard diet.

Scheme of the experiment was as follows: Group 1 – control. Healthy rats (intact control); group 2, 3 – rats, which modeled ABE 1st and 2nd degree, which was administered saline in the appropriate dose and timing (burn control); Group 3, 4 – ABE rats with 1st and 2nd degree, which was injected with melanin from the 2nd day of the experiment at a dose of 0.1 mg / kg for 14 days. Producers of melanin used in our studies were mushrooms Nadsoniella nigra strain X1 that sown with vertical rock samples o.Halindez. The method of removing animals from the experiment was cervical dislocation. To study plasma total proteolytic activity and determining the activity of serine proteases and metal obtained using 3.8 % sodium citrate at 7, 15 and 21 days [32].

The total proteolytic activity analyzed by method of caseinolytic activity with modifications. For determination selective activity of MMP and serine proteases to the reaction mixture (final concentration) was added 0.2 mol/l EDTA or PMSF, respectively. [9] 30 ml plasma argued 0.05 M (pH 7.4) phosphate buffer to a volume of 1 ml [33]. Was stirred and added to 1 ml of 4 % casein. Then incubated for 30 min. in a water bath at 37 C. The reaction was stopped by introducing 3 ml of 15 % CCl3COOH followed by centrifugation at 2000 rev. / min., 30 min. The supernatant was selected optical density measured at a wavelength of 280 nm. The control sample consisted of a mixture of casein, phosphate buffer and respective CCl3COOH in identical proportions. To prepare 4 % casein reagent sample weighing 4 grams dissolved in 80 ml 0.05 M phosphate buffer pH 7.4 and 1.6 ml 1M NaOH. The mixture is left at room temperature for 40 minutes. for swelling. Then boiled 15 minutes in a water bath. Once cooled, casein pH was adjusted to 7.4 and 1 M NaOH volume was adjusted to 100 ml phosphate buffer.

The statistical analysis of the obtained results was performed using the methods of variation statistics and correlation analysis using the computer program Excel. To determine the reliability of the differences between the two samples we used the Student test (t). Whereby differences $P < 0.05$ were deemed reliable.

Results. The progress of wound healing, after the chemical inflammation, is determined of interaction of different metabolic systems, as the organism, and as the contacting tissue. This process is controlled of the different kind of biochemical homeostasis support. Important role at the wound heling, have some proteolytic enzymes, that catalyze splitting of the protein molecules. Thus, these enzymes by nonspecific proteolysis, involved at the remove of the necrosis tissues. The progress of cicatrization, after inflammation wounds are the dynamical process, and are required some balance between mechanisms of synthesis and degradation of the ECM components. Proteolytic degradation of the ECM, are one of the crucial steps at the cicatrization of inflammation lesions, and are provided of the proteolytic enzymes [34].

The proteinases activity depends, from their appearance from inactive predecessors, and inactivating of the specific inhibitors, which are present in cells, tissues and blood plasm, and make anti-proteolytic potential [35]. At the critical states, are violated the dynamic balance between proteinases and their inhibitors, that are important

link of pathogenesis of the many diseases (pancreatitis, fibrosis, cancer, etc.) [36].

We have determined the overall activity of proteolytic enzymes in the rat's blood plasma at the different degrees of the ABE (Fig. 1).

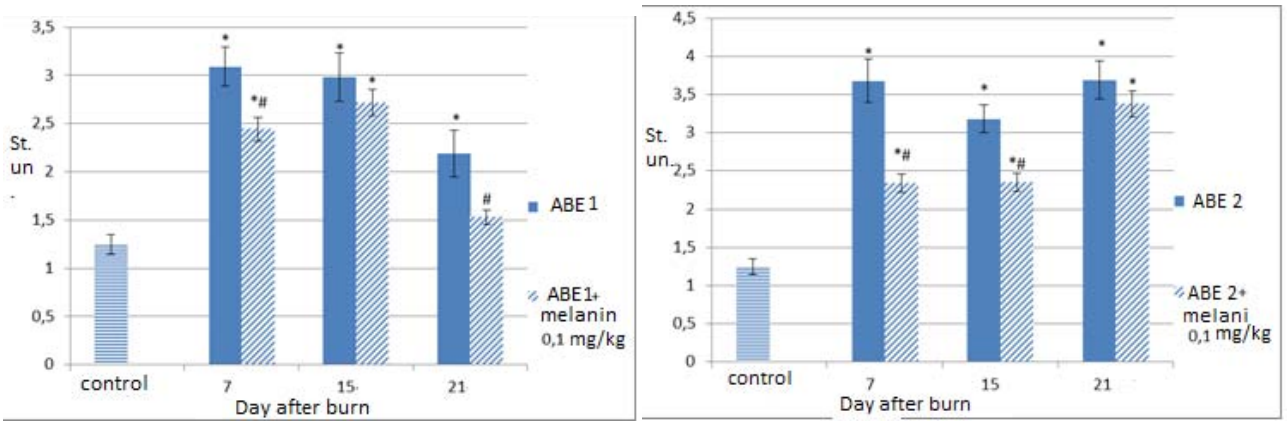

Fig. 1. The total proteolytic activity in plasma (caseinolytic units/mg protein) after experimental burn and under conditions administration of melanin (M±m, n=8)

Note : (*p<0,05 compared with control value, # p<0,05 compared with ABE 1st and 2nd degree).

Proteolytic activity increased at the first and second degrees of the inflammation, during of all of the experiment time. So, at the ABE 1st, activity was increased by 2.5 times on the 7th day, and by 2.3, 1.8 times on the 15th and 21st days. Melanin administered was decreased of the activity on the 7th, 15th and 21st days by 1.3, 1.1, and 1.4 times, in compared with the animals with first degree of ABE. At the second degree of ABE, was noted the growth of proteolytic activity at the all days of the experiment. On the 7th day by 2.9 times, on the 15th and 21th days by 2.5 and 2.95 times, in compared with intact control. At the melanin administered, was observed the trend to the decreased of the proteolytic activity, in compared with animals with inflammation, so on the 7th, 15th and 21st days activity was decreased by 1.6, 1.35 and 1.1 times.

Among the proteolytic enzymes, the most crucial are serine and metalloproteinase. Thus, increased of serine proteinase activity in the extracellular matrix, view as basic link of the many pathological states, at which there is infiltration of tissues by the neutrophils, which are accompanied of inflammatory reaction [37]. The most typical serine protease is the chymotrypsin, trypsin, plasmin, elastase, urokinase, kalikreine of blood plasma and some clotting factors [38]. From the references are known that crucial function of the MMP are degradation of the ECM complexes. But the new impetus to the most detail of the MMP function research, data become information that in addition to these destructive this MMP have regulatory function, making the processing of biological activity substances. MMP involved and control many process: cell proliferation, adhesion, migration, differentiation and apoptosis [39]. Therefore, we were studied activity of the serine protease and metalloprotease in rat's blood plasm with ABE (1st and 2nd degrees).

Metalloproteinase activity increased throughout the experiment (Fig. 2), at the ABE 1st degree the highest values were for 15th days, which exceeded the reference value by 2.3 times, while the ABE 2nd degree for 15th and 21st days where activity was higher by 2.4 and 2.76 times, respectively. With the used of melanin metalloproteinase activity decreased notably 15th days at ABE 1st degree by 1.4 times, the ABE 2nd degree by 1.47 times compared with animals that were burned esophagus.

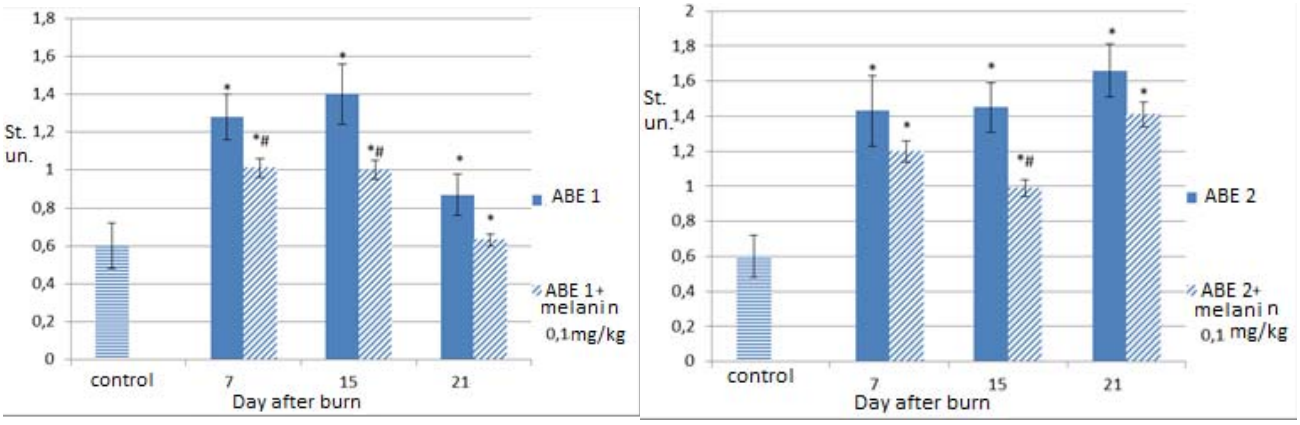

Fig. 2. Activity of MMP in plasma (caseinolytic units/mg protein) after experimental burn and under conditions administration of melanin (M±m, n=8)

Note: (*p<0,05 compared with control value, # p<0,05 compared with ABE 1st and 2nd degree).

The activity of serine proteases in the conditions of burn increased especially on 7th day of experiment (Fig. 3), which exceeded the reference value at ABE 1st degree by 3.5 times, the ABE 2nd by 4.7 times. In the conditions the used of melanin activity of serine proteases was decreased for ABE 1st degree at 7th day by 1.23 times and for ABE 2nd degree by 2 times compared with animals that were burned esophagus.

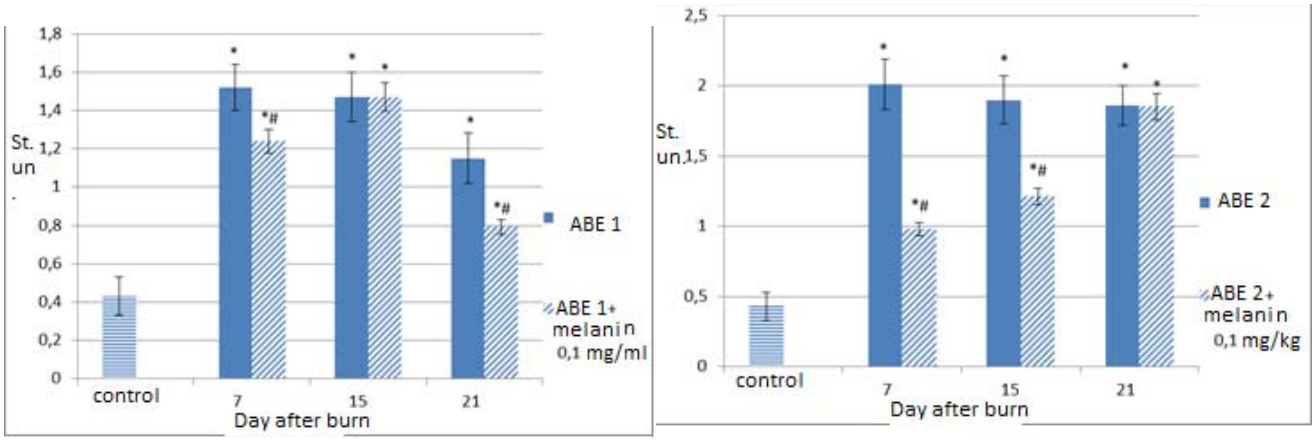

Fig. 3. Activity of serine proteinase in plasma (caseinolytic units/mg protein) after experimental burn and under conditions administration of melanin (M±m, n=8)

(*p<0,05 compared with control value, # p<0,05 compared with ABE 1st and 2nd degree)

Conclusion. Thus, a chemical burn of the esophagus 1 and 2 degrees led to a breach in the system proteolysis, increased general proteolytic activity and activity of certain proteases (matrix metalloproteinases and serine). In the conditions of first degree the most activity was at 7 and 15 days. While second-degree burns the most activity was 15 and 21 days. When using melanin at a dose of 0.1 mg / kg was observed a significant decrease of total proteolytic activity and activity of matrix metalloproteinases and serine, which may indicate the prospect of of its use in clinical practice.

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КОРЕКЦІЯ МЕЛАНІНОМ ПРОТЕОЛІТИЧНОЇ АКТИВНОСТІ ЗА УМОВ ЛУЖНОГО ОПІКУ СТРАВОХОДУ

За умов опіку стравоходу першого та другого ступенів відмічено підвищення загальної протеолітичної активності та активності основних протеїназ (серинової та металопротеїназ). Експериментальна корекція меланіном у дозі 0,1 мг/кг сприяла нормалізації патологічного зростання загальної протеолітичної активності та активності основних протеїназ (серинової та металопротеїназ), що вказує на нормалізацію стану системи протеолізу.

Ключові слова: лужний опік стравоходу, протеоліз, меланін.

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КОРРЕКЦИЯ МЕЛАНИНОМ ПРОТЕОЛИТИЧЕСКОЙ АКТИВНОСТИ В УСЛОВИЯХ ЩЕЛОЧНОГО ОЖОГА ПИЩЕВОДА

В условиях ожога пищевода первой и второй степени, было отмечено повышение общей протеолитической активности и активности основных протеиназ (сериновых и металлопротеиназ). Экспериментальная коррекция меланином в дозе 0,1 мг / кг способствовала нормализации патологического роста общей протеолитической активности и активности основных протеиназ (сериновых и металлопротеиназ), что указывает на нормализацию состояния системы протеолиза.

Ключевые слова: щелочной ожог пищевода, протеолиз, меланин.