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Editorial Article

Identification of the antitumor activity of biologically active components of viper venom and their effect on the formed elements of the blood of rats

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Abstract

Snake venoms are a unique group of biologically active compounds in their chemical composition and physiological effects.

The purpose of this work was to study and identify the antitumor activity of the biologically active components of the venom of the viper Macrovipera lebetina obtusa and their effect on the formed elements of the blood of experimental animals.

The experiments were carried out on 25 white outbred white laboratory rats (males) weighing in the range of 200-220 g, in which pathological changes were detected in the body. Experimental animals were administered intravenously a complex of biologically active components of viper venom at a dose of 0.02 mg/kg body weight of the test animal with manganese nanoparticles.

Research methods and their results. Laboratory blood tests were performed using an Auto Hematology Analyzen Ratyo RT -7600 apparatus. The activity of enzymes - ALT and AST, ALP, γ-GTP, lactate dehydrogenase (LHD) was carried out using reagent kits produced by "HUMAN" on a BIOSKREM MS 2000 microanalyzer, manufactured in the USA. The content of leukocytes in the blood increased by 45%, lymphocytes decreased by 12%, granulocytes, monocytes and neutrophils increased by 8.2%, 3.5%, 3.7%, respectively. Hemolysis and free hemoglobin were not detected in the blood. Compared to the control group, cHCO3 blood levels increased by 1.7%; cBase (Ec) - decreased by 2.5%; cLac increased 2.8%. The K+ content decreased to 3.1 mmol/L from 3.7 mmol/L in the control group, and Na+ increased to 131 mmol/L from 108 mmol/L. Hypoproteinemia up to 48 g/l was detected in the blood of animals of group 2. In the blood serum of animals, the content of ALT and AST increased by 2.8 and 1.4 times, γ-GTP, LDH, ALP increased by 37.5%, 16.2%, 96.8%, respectively, TB, MMP and CRP increased by 2.8, 1.3 and 2.4 times respectively, and TP decreased by 41%, HP, DK, MDA increased by 2.3, 2.3 and 2.0 times, while OAC, Kat, SOD decreased by 43. 7%, 36.3% and 29.2%, LDH, VLDL, TC, TQ increased by 4.7, 3.6, 3.2, 1.5 times, while HDL decreased by 1.6 times. Laboratory research data confirmed that all determined indicators practically reached intact values after 72 hours. Thus, it was revealed that with a daily (one-time) injection of both a mixture of whole venom with manganese nanoparticles and a mixture of bioactive components of viper venom in doses of 2 mg/kg or 20 μg/mouse with manganese nanoparticles, a significant decrease in the intensification of tumor cell activity in the body of experimental animals was observed.

Keywords: venom; viper; Macrovipera lebetina obtusa; leukocytes; erythrocytes; tumor cells; manganese nanoparticles

Introduction

Snake venoms, which are a complex mixture of peptides and proteins, act on various vital systems of the body, which makes them very valuable as a basis for the creation of new effective drugs with a given pharmacological activity. The main disadvantages of toxins are high toxicity and irreversible action, i.e., the impossibility of returning the system on which they acted to its original state.

The study of poisonous products of the biosynthesis of snakes, which are a unique group of biologically active substances in their chemical composition and physiological action, and the elucidation of the pharmacological activity of individual components of snake venom is an urgent problem of modern medical and biological science. Zootoxins are a complex complex of various substances. They contain proteins, lipoproteins, peptones, mucin and mucin-like substances, purine bases, salts, various trace elements, and remnants of epithelial cells. However, the main component of snake venom, responsible for most of its toxic properties, are biologically active components of a protein nature, as well as various enzymes [1, 2, 3].

Conflicting data were obtained from experimental studies of the effect of snake venoms on malignant neoplasms in animals. Karimov Z.N. [4] found that cobra venom, when administered intravenously to rats, causes an average antitumor effect against sarcoma 45 and M-1; Viper venom, when administered intravenously or intramuscularly, has weak antitumor activity.

Kasenova K.U. and Kunaeva K.S. [5,6] noted that the venoms of snakes of the viper, pit viper and asp families cannot be classified as antitumor forms. The authors recommend the use of snake venoms in oncology as analgesics. It is also known that protein components isolated from cobra venom selectively act on tumor cells without affecting normal cells [7].

From the contradictory data it follows that the use of snake venoms in antitumor therapy requires additional research.

Malignant neoplasms have become a leading topic of research in medicine and veterinary medicine.

To diagnose the presence of cancer in rodents, modern methods are used, and a number of studies are also carried out, among which are: blood tests using ultrasound, ECG, CT and MRI.

The occurrence of neoplasms is promoted by many reasons. Tumors are very rare in young animals. After 2 years of life, tumors are diagnosed in every 4 individuals. The intensity and nature of the tumor depends on the characteristics of the organism, the level of resistance of the affected tissue, histological and biological characteristics of the tumors. A complex of factors influences the increase in size, and it can occur over a period of days, weeks or months. It is almost impossible to predict growth; it is known that stress, depression and trauma accelerate defeat.

To determine the presence of cancer in a rat, the following types of diagnostics are used: palpation and visual examination, x-ray examination; ultrasonography; blood analysis; analysis for histo- or cytology [8].

The study of integral indicators characterizing the differences between biological samples obtained from healthy and sick people is of great importance, since diagnostics based on a single marker are often uninformative [9,10]. Raman spectroscopy is a powerful analytical method that can be used in the differential diagnosis of diseases. Spectrum Raman spectroscopy provides a molecular fingerprint of a sample and provides quantitative information about its chemical composition. Biochemical changes in cells and tissues associated with various diseases can lead to significant changes in Raman spectra [11-13].

Blood testing can provide minimally invasive diagnostics for many diseases, including cancer. Any disease, pathological process, as well as a number of physiological changes can, to one degree or another, affect the quantitative and qualitative characteristics of the composition of circulating blood. This determines the great importance of the need to study blood. White blood cells, having high reactivity, quickly become involved in adaptive reactions. They are capable of nonspecific reactions in response to alternating influences [14].

Blood components contribute to the general condition of the body system. Blood serum contains almost 90% water, about 6.6−8.5% proteins and other organic and mineral compounds, which are intermediate or final products of metabolism carried by the blood. Various blood components have a significant impact on Raman spectra, and their contribution can change with the development of pathological conditions [15,16]. In the range of 500-1800 cm-1 there are a large number of lines, individual for each organic compound [17]. This is mainly the region of stretching and bending vibrations. Based on the presence or absence of specific lines in the spectrum in this range, one can determine both the substance under study and its concentration in a biological sample [18].

From the numerous and contradictory studies available on the use of snake venoms, it follows that they have far from the same pharmacological properties, being of great value for clinical and experimental medicine. Thus, the results of treatment of malignant tumors with venom are assessed differently by different authors, but positively all researchers come to the unanimous conclusion that snake venom has a well-defined effect, improves overall metabolism and thereby helps to increase the body's activity in the fight against malignant neoplasms.

Irish scientists John and Paul Reed created a drug based on a specific protein extracted from frozen rattlesnake venom. However, the venom of not every subspecies is healing, but exclusively of Crotalus durissus terrificus, which lives in the Reptile Zoo in Kentucky (USA). According to the scientist brothers, the drug acts selectively on pathological tumor cells and does not harm healthy ones. In 2011, they began practical experiments on animals, after which they tested their medicine on six volunteer patients in France [19].

Scientists have been studying crotoxin, a component of the venom of one of the South American rattlesnakes, for more than a hundred years. This substance has been found to have analgesic, anti-inflammatory and antitumor properties, but its high toxicity has so far prevented its use in medicine. The new method makes it possible to reduce the toxic effects of the substance and at the same time enhance its therapeutic effect [20].

The literature provides experimental data on identifying the influence of environmental pollutants on snake venoms, including the venom of the viper. However, despite the comprehensive study of snake venom, many issues remain insufficiently studied and require in-depth analysis and more detailed study [21-31].

On the other hand, over the past decade, scientists have created several fundamentally new methods for treating cancer and other diseases, which are based on the action of various organic or inorganic nanoparticles. In some cases, these structures are directly involved in destroying the tumor or eliminating the source of the disease. They

serve as unique “targets” that are targeted either by immune cells or by laser radiation [32].

Since direct injection is not possible for some types of malignant tumors, the nanoparticles are injected into a vein or abdominal cavity. Russian scientists have created a new type of nanoparticles based on iron, zinc and manganese that can “burn out” cancerous tumors when interacting with a magnetic field without killing healthy cells. Nanoparticles serve only as a means of delivering drugs and toxins to the tumor [33].

For treatment to be effective and safe, it is necessary to ensure that the tumor temperature falls within the range of 42–52 °C. The size, physical properties and concentration of nanoparticles, as well as methods of their synthesis, are also important. However, magnetic hyperthermia itself has very limited application in clinical oncology. At the same time, it is very difficult to control the distribution of particles in the tumor itself. The method is not designed for radical treatment of most malignant neoplasms [34].

Based on the above, the purpose of this work was to study and identify the antitumor activity of the biologically active components of viper venom and their effect on the blood cells of rats using manganese nanoparticles, determining the activity of enzymes - ALT and AST, ALP, γ-GTP, lactate dehydrogenase (LHD total blood protein (TR), total bilirubin (TB), medium molecular peptides (MMP), C-reactive protein (CRP), products of lipid peroxidation (LPO) - hydroperoxide (HP), concentration of diene conjugates (DK), malondialdehyde (MDA), total antioxidant status (TAS), catalase (Kat) and superoxide dismutase (SOD) activity

Materials and methods of research

The experiments were carried out on 25 white outbred white laboratory rats (males) weighing in the range of 200-220 g, in which pathological changes were detected in the body. All animals used in the experiments were kept under the same conditions of care and diet. Animal experiments were carried out in accordance with the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes, Strasbourg, 1986.

The animals were divided into 3 groups: Group 1 – control (5 rats), which were injected with saline solution intravenously. Groups 2 and 3, 10 rats each, which were intravenously injected with a complex of biologically active components of viper venom at a dose of 0.02 mg/kg body weight of the test animal with manganese nanoparticles. Experimental animals were decapitated 24 hours (2nd group) and 72 hours (3rd group) after intravenous injection of poison, followed by blood sampling for laboratory studies.

Laboratory blood tests were carried out using an Auto Hematology Analyzen Ratyo RT -7600 device, made in China, 2019. Quantitative indicators of erythrocytes, leukocytes, lymphocytes and platelets were determined in the blood of experimental animals as the most informative indicators of the blood being tested.

The work used a method of inducing hyperthermia using high-frequency magnetic field, which is applied to the tumor with the capture of exogenous nano-sized particles in it [35]. This technique generates local heat near a magnetic nanoparticle around the tumor in a time-varying magnetic field, which occurs due to the transfer of energy from the external magnetic field into heat. As a result, tumor cells are heated to the Curie temperature, while benign tissue is preserved. This method ensures uniform heating and destruction of tumor tissue and reduces the side effects of magnetic nanoparticles.

The activity of enzymes in the blood was also determined - ALT and AST, ALP, γ-GTP, lactate dehydrogenase (LHD), which was carried out using reagent kits produced by "HUMAN" on a BIOSKREM MS 2000 microanalyzer, manufactured in the USA. Blood content of total protein (TP), total bilirubin (TB), medium molecular peptides (MMP), C-reactive protein (CRP), products of lipid peroxidation (LPO) - hydroperoxide (HP), concentration of diene conjugates (DK), malonic dialdehyde (MDA), total antioxidant status (TAS), catalase (Kat) and superoxide dismutase (SOD) activity were determined on a BIOSKREM MS 2000 microanalyzer, manufactured in the USA, using reagent kits manufactured by “HUMAN”.

The content of triglycerides (TQ), total cholesterol (TC), low-density lipoproteins (LDL), intermediate-density lipoproteins (VLDL), high-density lipoproteins (HDL) was determined by the enzymatic colorimetric method using a set of chemical reagents produced by Human, Germany. Determinations were carried out on an FP-9019 analyzer (made in Finland). An electrocardiogram was performed using an Elektrocardigraph Carawell ECG-II03GVet device, made in China.

The research material was the whole venom of the Transcaucasian viper (Macrovipera lebetina obtusa), dried in a desiccator over calcium chloride vapor. The poison of the viper was dissolved in a 0.9% solution of sodium chloride, followed by the isolation of biologically active components that have a destructive effect on tumor tissue. Experimental animals were administered intravenously with a solution of a complex of biologically active components of the poison and iron oxide nanoparticles

Statistical analysis of quantitative data was carried out using nonparametric methods - the Wilcoxon-Mann-Whitney test. When studying the dependencies between indicators, the Spearman formula for the rank correlation coefficient was applied:

where: d – difference of ranks, n – number of ranks.

When applying the above methods, MS EXCEL and S-PLUS programs were used for statistical processing.

Таблица 1.

Results and their discussions

The results of laboratory studies showed that significant changes occur in the content of leukocytes and erythrocytes in the blood, which do not pose a threat to the body of experimental animals and contribute to the gradual improvement of their physiological condition.

After intraperitoneal injection of viper venom at a dose of 0.02 mg/kg body weight with manganese nanoparticles into a cancerous tumor and exposed to a magnetic field, heating it to a temperature of 42 °C, supraventricular extrasystoles, occasional group extrasystoles, and

conduction disturbances along the right bundle branch were noted on the ECG. Atriventricular conduction slowed down, and a first-degree block was noted.

Laboratory blood tests indicated leukocytosis, lymphopenia, monocytosis, and granulocytosis. The content of leukocytes in the blood increased by 45%, lymphocytes decreased by 12%, granulocytes, monocytes and neutrophils increased by 8.2%, 3.5%, 3.7%, respectively. The changes are statistically significant at $P<0.05$. Hemolysis and free hemoglobin were not detected in the blood (tabl.1).

Table 1.

Indicators of general blood test in rats are normal and after intraperitoneal injection of viper venom with manganese nanoparticles

General blood test indicators	Control group	Experimental group
lymphocytes	55 – 77 %	67-89%
granulocytes	31-33%	39.2-41.2%
monocytes	1– 5 %	3.5-8.5%
neutrophils	12 – 31 %	15.7-34.7%

Metabolic acidosis was observed in the blood. Compared to the control group, cHCO3 blood levels increased by 1.7%; cBase (Ec) - decreased by 2.5%; cLac increased 2.8%. The K+ content decreased to 3.1 mmol/L from 3.7 mmol/L in the control group, and Na+ increased to 131 mmol/L from 108 mmol/L. Hypoproteinemia up to 48 g/l was detected in the blood of animals of group 2.

In the blood serum of animals, the content of ALT and AST increased by 2.8 and 1.4 times, γ-GTP, LDH, ALP increased by 37.5%, 16.2%, 96.8%, respectively, TB, MMP and CRP increased by 2.8, 1.3 and 2.4 times respectively, and TP decreased by 41%, HP, DK, MDA increased by 2.3, 2.3 and 2.0 times, while OAC, Kat, SOD decreased by 43. 7%, 36.3% and 29.2%, LDH, VLDL, TC, TQ increased by 4.7, 3.6, 3.2, 1.5 times, while HDL decreased by 1.6 times. All changes are statistically significant at $p <0.001$ and $p <0.01$. The data obtained confirm the development of hepatitis in animals. Subsequently, the condition of the animals improves. Laboratory research data confirmed that all determined indicators after 72 hours practically reached intact values (group 3).

Integral indicators, including data on weight changes, food and water consumption, assessment of the general condition of the animals' motor activity and respiratory rate showed that after the introduction of a mixture of bioactive components of viper venom with manganese nanoparticles, the animals showed restless behavior on the first day, then calmed down and behaved according to the species characteristics.

The data obtained allow us to assert that the combined use of viper venom with manganese nanoparticles reduces the overall toxicity of the poison and makes it possible to use it as a pharmacological agent, in particular in the treatment of neoplasms. A study of individual components of viper venom as well as manganese nanoparticles showed that they have an inhibitory effect on a number of kinases involved in tumor development. Therefore, we consider research in this direction promising with the goal of creating a new generation of chemotherapeutic agents based on zootoxin.

Thus, the results of a study of the antitumor properties of viper venom demonstrate the undoubted presence of antitumor activity, preventing the growth and division of cancer cells, and it is important to note that these effects were achieved, as a rule, using low doses and concentrations of zootoxin and in many cases were very pronounced.However, it remains to establish the in vivo activity of these proteins and to determine their stability and their activity in the body that contributes to the recovery of experimental animals. To date, there are no data on clinical studies of these proteins. In conclusion, it should be noted that, despite the existing shortcomings, a number of peptides and proteins of viper venom that affect the blood have good prospects as a basis for the creation of new drugs with anticancer activity.

Conclusions

1. Presumably, the antitumor properties of the complex of bioactive components of viper venom with manganese nanoparticles have been identified.
2. It was revealed that the complex of bioactive components of viper venom with manganese nanoparticles can become the basis for the synthesis of new effective drugs with antitumor activity, causing a stop and slowdown in the growth of malignant tumors by blocking tumor cell receptors.
3. The use of a magnetic suspension in the viper venom extract and exposure to a magnetic field until the temperature reached 42°C in the tumor area led to increased destruction of tumor cells, while the surrounding tissues were preserved.

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