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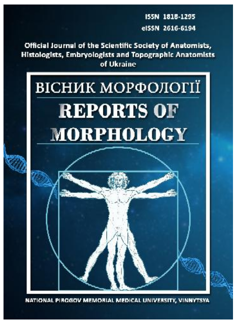

Analytical and quantitative assessment of the structural components of the adrenal glands of rats under the conditions of exposure to the venom of vipers Vipera berus berus and Vipera berus nikolskii

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Snakebite envenoming is a common but neglected public health problem worldwide, especially in tropical countries. Annual mortality as a result of snakebites exceeds 138,000. It is believed that this problem is underestimated, and in many countries, individual cases of bites are not subject to proper fixation. The purpose of the study is the analytical and quantitative assessment of the structural components of the rats' adrenal glands under exposure to the venom of Vipers Vipera berus berus and Vipera berus nikolskii. Experimental studies were carried out on white, non-linear male rats. Vipera berus berus and Vipera berus nikolskii viper venom were obtained from V. N. Karazin Kharkiv National University. The freeze-dried native venom was stored at -20 °C and dissolved in saline immediately before the experiment. The animals were divided into three groups (control and 2 experimental groups) of 10 individuals each. Experimental rats were injected intraperitoneally in a physiological solution with a semi-lethal dose (LD50) (1.576 mg/g^{-1}*) of Vipera berus berus and Vipera berus nikolskii venoms. Animals of the control group were injected intraperitoneally with only a physiological solution. Rats were removed from the experiment 24 hours after exposure to the poison and anesthetised by cervical dislocation. Statistical analysis of the area of the microcirculatory channel and the nuclear-cytoplasmic index was performed using Fiji: ImageJ program and processed in Excel. Administration of the venom of the vipers Vipera berus berus and Vipera berus nikolskii to rats was accompanied by a significant increase in the area of the microcirculatory bed relative to the control group (2.9 times for Vipera berus berus and 6.5 times for Vipera berus nikolskii). Exposure to Vipera berus berus viper venom was associated with a significant decrease in the nuclear-cytoplasmic index in rats of the experimental group compared to the control group (13 % and 42 %, respectively), which is evidence of a decrease in the area of the nuclei of endocrinocytes of the adrenal cortex. This indicator in rats under the administration of Vipera berus nikolskii venom was even lower and amounted to 12 %. According to the statistical analysis of the quantitative assessment of the state of the cortical substance of the adrenal glands, it is worth noting the similar effect of the poisons of both types of snakes at the cellular level. At the same time, at the tissue level, the effect of Vipera berus nikolskii venom is more pronounced than that of Vipera berus berus - this is evidenced by the higher degree of disruption of the structure of the hemomicrocirculatory channel in the adrenal cortex of animals from the group that was affected by this venom. It led to an increase in the area of vessels due to their expansion and ruptures of their walls and haemorrhages into the surrounding parenchyma and stroma.*

***Keywords:** vipers, poison, nuclear-cytoplasmic index, microcirculatory channel, rats.*

Introduction

Envenomation from the bites of snakes and other venomous animals, including scorpions, is a common but neglected public health problem worldwide, especially in tropical countries [23, 29]. Annual mortality from snake bites exceeds 138,000, and mortality from scorpion bites reaches 1.5 million cases [9, 12, 13]. It is believed that this problem is underestimated, and in many countries, individual cases of bites are not subject to proper fixation [15, 39]. In India, about 58,000 people die each year from complications caused by snake and in particular viper venom [33].

It is known that the toxins of snakes and vipers are a complex mixture of proteins, peptides, low molecular weight substances, and salts in the water environment [10, 19]. Usually, venom causes a neurotoxic effect, local destruction of soft tissues in the places of its inoculation, or a vasohemotoxic effect [24, 31]. These data correlate with the mechanism of action of scorpion venoms, in which the severity of envenomation is closely related to the neurotoxic effects of the venom (excitation of neurons and release of catecholamines). However, developing severe systemic disorders may be associated with increased enzymatic activity in tissues, which also activates the inflammatory response [11]. Clinical manifestations are diverse and include local (oedema, tissue necrosis) and systemic [14, 34]. The latter is manifested in the form of neuromuscular paralysis, rhabdomyolysis, hypotension, collapse, and DIC syndrome [37, 38].

In recent years, scientists have reported the development of endocrine and metabolic disorders as a result of pituitary dysfunction, adrenal gland damage, dysglycemia, electrolyte disturbances, and renal tubular acidosis [21, 26, 36].

The endocrine system, which has a wide range of hormonal influences on various organs and systems, plays an extremely important role in the emergence of body reactions to stimuli [5, 8]. At the same time, not individual hormones but the overall endocrine balance, which is formed in a state of stress and tension, determines the nature and strength of compensatory-adaptive and protective processes for adaptation and resistance of the organism [28, 27].

Adrenal glands occupy an important place in the endocrine regulation of the human body's vital processes in a changing environment. It is a well-known fact that the adrenal glands participate in the mechanisms of adaptation of an individual to stress of exo- or endogenous origin [18, 35]. Their role has also been established in regulating water-mineral balance and the synthesis of biomolecules (proteins, fats, carbohydrates). It should be noted that in response to the action of a stressor, the adrenal glands ensure adaptation and the development of compensatory and adaptive changes in organs and systems [20, 30]. The formation of these mechanisms is possible mainly due to the influence of epinephrine and glucocorticoids, the level of which is a determining factor for the degree of expressiveness of the body's reaction and the development of morphological changes in organs [7, 16].

Considering the above facts, studying the qualitative and quantitative composition of the adrenal glands and cellular components of rats under *Vipera berus* berus and *Vipera berus* nikolskii venom is an urgent task.

The research aims to analyse and quantitatively assess the structural components of the adrenal glands of rats under exposure to the venom of *Vipera berus* berus and *Vipera berus* nikolskii.

Materials and methods

Experimental studies were carried out on white, non-linear male rats. For preliminary acclimatisation, the animals were kept for 7 days in the animal facility of Taras Shevchenko National University of Kyiv, and later - in laboratory conditions with compliance with temperature and light regimes [3]. Rats received standard chow and water ad libitum. All experiments were conducted in accordance with the National Institutes of Health Guidelines for the care and use of laboratory animals and the European Council Directive of 24 November 1986 for the Care and Use of Laboratory Animals (86/609/EEC). The research was approved and confirmed by the Bioethics Commission of the NSC "Institute of Biology and Medicine" of the Taras Shevchenko National University of Kyiv (protocol No. 2, dated August 19, 2021).

Vipera berus berus and *Vipera berus nikolskii* venom were obtained from the V. N. Karazin Kharkiv National University. The lyophilised crude venom was stored at - 20 °C and dissolved in a saline solution immediately before the experiment.

The animals were divided into a control and 2 experimental groups of 10 individuals each. Experimental rats were injected intraperitoneally with a semi-lethal dose (LD50) (1.576 mg/g^{-1}) of *Vipera berus berus* and *Vipera berus nikolskii* venom in saline solution. Animals in the control group were injected intraperitoneally with only a saline solution. Rats were removed from the experiment 24 hours after exposure to the venom and anesthetised by cervical dislocation.

The statistical analysis of rat adrenal gland parameters evaluated two continuous variables: the microcirculatory bed's area in these glands' stroma and the nuclear-cytoplasmic index of hormone-producing cells in their parenchyma. These parameters were determined for one control group and two experimental groups, in which rats were exposed to the venom of two vipers - *Vipera berus berus* and *Vipera berus nikolskii*. All measurements were made using the Fiji: ImageJ program and processed in Excel.

In order to estimate the share of the adrenal glands occupied on the sections by elements of the microcirculatory channel, we measured the area of the corresponding vessels in 8 sections of the adrenal glands of animals from the control and two experimental groups (four animals from each group). Next, we calculated the sum of these areas for each slice. Digital images obtained under a light microscope at a magnification of x1000 were used for measurements. The section area within which vessels were measured for all groups is 23803 μm^2.

In order to quantitatively assess the general condition of adrenal parenchyma cells, we calculated the nuclear-cytoplasmic ratio in the endocrine cells of the zona glomerulosa and zona fasciculata of the cortex.

The nuclear-cytoplasmic index was calculated in 40 cells on 4 sections from four animals from each group. Measurements were performed on digital images obtained from a light microscope at x1000 magnification.

Since when checking the measurements of the control and both experimental groups for normality of distribution, the graphs did not correspond to the Gaussian curve, the non-parametric Mann-Whitney test was used to determine the reliability of the differences between the groups [17].

Results

When analysing the total area of the microcirculatory channel of the cortex, which is occupied by small vessels on the sections of the adrenal glands, a significant increase of this index was found in the group with the injection of Vipera berus berus venom compared to the control group (Table 1). If in the control group, this index is 445.3 μm^2 (first quartile 318 μm^2; third quartile 512 μm^2), then for the corresponding experimental group, it is 1298 μm^2 (first quartile 915 μm^2; third quartile 1615 μm^2).

This expansion of the microcirculatory bed is quite logical and is related to several factors. First, venom damages the walls of blood vessels as it is transported with the blood. Formal blood elements are affected, particularly erythrocytes, which aggregate and clog vessels. Snake venom primarily affects proteins, including blood plasma proteins, coagulating them and thus disrupting the structure and viscosity of blood. In addition, the arrival of a foreign factor to the tissues and its spread there provokes the development of inflammatory reactions, accompanied by swelling of the tissues, expansion of blood vessels and increased permeability.

It is worth noting the insignificant standard deviation for both groups, which indicates the regularity of the processes of vessel expansion, which is equally inherent to all elements of the microcirculatory channel (Fig. 1). It can be assumed that the venom of Vipera berus berus damages the microcirculatory processes in the adrenal gland, which leads to a violation of its morphology and functioning and, ultimately, to necrosis. Because we assessed the adrenal glands 24 hours after venom administration, the tissue changes are not radical, and the vascular damage will likely worsen over time.

The assessment of the condition of the vessels of the microcirculatory bed in the group with the introduction of *Vipera berus nikolskii* venom showed a significant increase in the area of the microcirculatory bed of the animals compared to the control group (Fig. 1). Here, this indicator is 2916 μm^2 (first quartile 1533 μm^2; third quartile 3884 μm^2).

Table 1. The average value of the microcirculatory channel area of the adrenal glands in the control and experimental groups (M±σ).

Group	The average value of the area, mm^2	The presence of a reliable difference with the control group
Control group	445.3±226.5	-
Group with an injection of Vipera berus berus venom	1298±608	Present*
Group with an injection of Vipera berus nikolskii venom	2916±1655	Present*

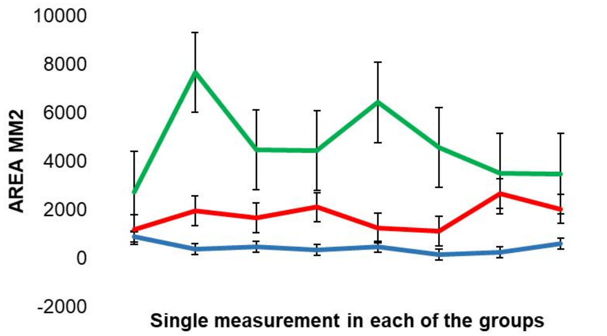

Fig. 1. Individual indexes of the area of the microcirculatory bed of animals of the control and experimental groups with standard deviation. Green colour - control group; red colour - the group with the injection of *Vipera berus berus* venom; blue colour - the group with the introduction of *Vipera berus nikolskii* venom; I - standard deviation.

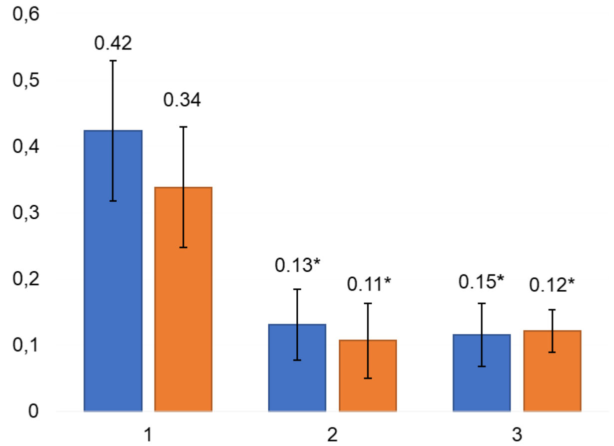

Fig. 2. The average value of the nuclear-cytoplasmic index in the adrenal cortex cells in the control group, the group with the injection of *Vipera berus berus* venom and *Vipera berus nikolskii* venom. 1 - control group; 2 - a group with an injection of *Vipera berus berus* venom; 3 - a group with an injection of *Vipera berus nikolskii* venom; blue columns - zona glomerulosa; orange columns - zona fasciculata; * - the difference from the control group is significant at $p \leq 0.05$.

The vessels of the adrenal cortex increase in size due to swelling and disruption of their content. The lumens of capillaries and venules expand due to the accumulation of aggregated erythrocytes and blood plasma clots in them. Similar processes are observed under the action of *Vipera berus berus* venom. Although we did not find a reliable

Table 2. Nuclear-cytoplasmic index of endocrinocytes of the adrenal cortex in control and experimental groups.

Group	Control group		The group with injection of *Vipera berus berus* venom		The group with injection of *Vipera berus nikolskii* venom	
Zone	Glomerulosa	Fasciculata	Glomerulosa	Fasciculata	Glomerulosa	Fasciculata
1	0.23	0.48	0.12	0.21	0.14	0.08
2	0.33	0.27	0.2 1	0.23	0.23	0.14
3	0.56	0.43	0.09	0.23	0.15	0.11
4	0.68	0.28	0.15	0.23	0.09	0.07
5	0.50	0.43	0.08	0.18	0.13	0.11
6	0.36	0.37	0.10	0.16	0.09	0.08
7	0.34	0.48	0.18	0.10	0.15	0.14
8	0.47	0.37	0.16	0.10	0.14	0.15
9	0.34	0.42	0.17	0.19	0.12	0.16
10	0.31	0.42	0.11	0.21	0.09	0.18
11	0.35	0.23	0.26	0.10	0.07	0.14
12	0.42	0.28	0.09	0.13	0.09	0.15
13	0.63	0.29	0.19	0.07	0.10	0.15
14	0.26	0.21	0.20	0.11	0.06	0.14
15	0.46	0.28	0.11	0.08	0.08	0.11
16	0.55	0.21	0.19	0.05	0.03	0.14
17	0.43	0.22	0.17	0.07	0.10	0.13
18	0.41	0.50	0.10	0.06	0.07	0.12
19	0.39	0.42	0.22	0.08	0.13	0.08
20	0.49	0.21	0.24	0.06	0.13	0.18
21	0.53	0.42	0.12	0.07	0.11	0.14
22	0.23	0.29	0.09	0.12	0.17	0.12
23	0.39	0.33	0.05	0.07	0.14	0.12
24	0.34	0.30	0.07	0.08	0.10	0.12
25	0.38	0.27	0.10	0.09	0.09	0.11
26	0.27	0.23	0.09	0.09	0.08	0.19
27	0.48	0.24	0.15	0.12	0.06	0.15
28	0.56	0.43	0.12	0.07	0.11	0.13
29	0.31	0.36	0.09	0.09	0.11	0.07
30	0.41	0.32	0.043	0.12	0.09	0.16
31	0.43	0.26	0.20	0.05	0.08	0.14
32	0.44	0.25	0.12	0.07	0.07	0.10
33	0.38	0.33	0.12	0.05	0.12	0.14
34	0.48	0.38	0.08	0.10	0.13	0.13
35	0.43	0.51	0.13	0.08	0.11	0.08
36	0.52	0.32	0.14	0.09	0.22	0.08
37	0.58	0.29	0.04	0.05	0.10	0.11
38	0.45	0.35	0.09	0.06	0.12	0.09
39	0.44	0.53	0.17	0.06	0.26	0.08
40	0.35	0.34	0.08	0.08	0.20	0.05

difference between the two experimental groups, the larger value of the average area of blood vessels in the group exposed to the Vipera berus nikolskii venom is worth noting. In addition to the pathological processes that develop as a result of the action of both venoms, the impressive action of the toxins causes the rupture of the wall of small vessels and the release of formal elements and blood plasma from them into the surrounding interstitium and parenchyma.

The value of the nuclear-cytoplasmic index conveniently assesses the influence of toxic substances on the morphology and functioning of cells since this parameter reflects the state of the nucleus, as a participant in protein synthesis, and the cytoplasm, in which most of the processes important for the functioning of the entire tissue and organ take place. In the case of an endocrine gland, the main process in the cytoplasm of parenchyma cells is the synthesis of hormones. Since we focused our attention precisely on the zona glomerulosa and zona fasciculata of the adrenal cortex, we are talking about the synthesis of steroid hormones, so the main part of the cytoplasm is occupied by a smooth endoplasmic reticulum and lipid droplets, which are the source of hormone synthesis.

Indexes of the nuclear-cytoplasmic ratio of zona glomerulosa cells of the adrenal cortex from the control group form a series with a slight standard deviation, indicating the homogeneity of differentiated endocrinocytes morphology (Table 2). This index averages 42 % for the control group (first quartile 35 %; third quartile 49 %), which is explained by the active functioning of these cells - their nuclei are large and bright, the cytoplasm is quite compact (Fig. 2).

In zona glomerulosa of the adrenal cortex of the group injected with *Vipera berus berus* venom, the nuclear-cytoplasmic index deviates significantly from the average value (Table 2) and is significantly lower than this index in the control group (see Fig. 2). The average value of the index in this group is 13 % (first quartile 9 %; third quartile 17 %). Such a low index indicates a decrease in the area of the nucleus, which is probably caused by its pyknosis because karyopyknosis accompanies the early stages of cell necrosis due to the action of external toxic factors. At the same time, the expansion of endoplasmic reticulum cisternae in the cytoplasm of cells leads to its vacuolisation. The expansion of the cisternae is related to the detoxification function of the endoplasmic reticulum in the cell, and the vacuoles increase the total area of the cytoplasm.

Let's talk about the group with the introduction of Vipera berus nikolskii venom. The pathological effect of this venom is manifested in a decrease in the nuclear-cytoplasmic index in zona glomerulosa cells (see Table 2). The average value of this index here is 12 % (first quartile 8 %; third quartile 14 %), which is significantly less than such index in the control group.

The decrease in the nuclear-cytoplasmic index in both experimental groups is proportional (Table 2), indicating that 24 hours after venom injection, their effect on this parameter is equally negative. Vacuolisation of the cytoplasm and condensation of the nucleus leads to a decrease in the functionality of the cells of zona glomerulosa of the adrenal cortex and a violation of normal metabolism.

A comparison of the nuclear-cytoplasmic index of the endocrinocytes of zona fasciculata of the adrenal cortex demonstrates a significant decrease of this index in both experimental groups relative to the control group (see Fig. 2). For the control group, the average value of this index is 34 % (first quartile 28 %; third quartile 42 %). The third of the cell, occupied by the nucleus, indicates the active work of these endocrinocytes in the production of cortisol and other glucocorticoids - the nucleus has a predominance of euchromatin and is quite large, the cytoplasm is enriched with lipid inclusions, which are a source of steroids for the synthesis of these hormones.

In the group with the introduction of *Vipera berus berus* viper venom, a number of indexes of nuclear-cytoplasmic ratio demonstrate its decrease (see Table 2). The average value of this index is 10 % (first quartile 7 %; third quartile 12 %), which is 3 times less than the index of the control group. Such a difference shows not only the vacuolisation of the cytoplasm but also the development of oedema in it, which is a manifestation of necrotic processes in endocrinocytes.

A decrease in the nuclear-cytoplasmic index in the group with the introduction of *Vipera berus nikolskii* venom is similar (see Table 2). Here, this index averages 12 % (first quartile 10 %; third quartile 14 %) and is also significantly different from the control group (see Fig. 2). Such a similarity in this index between the venoms of both vipers indicates that at the cellular level, their action is equally manifested already 24 hours after their entry into the body - probably the energy exchange in the cell is disturbed, which leads to the disorganisation of the work of ion pumps and the subsequent influx water into the cell, due to which its cytoplasm swells. Quantitatively, this is reflected in the nuclear-cytoplasmic index, and functionally, it results in a decrease in the ability of these cells to produce glucocorticoids.

Discussion

Measurement of the microcirculatory bed area was chosen to analyse the effect of viper venom on the adrenal glands because the bloodstream carries toxic substances and, obviously, harms the vessel walls and intravascular elements, such as plasma and formal blood elements. The total area of arterioles, capillaries and venules present in the sections of these endocrine organs can quantitatively characterise such pathological processes as oedema, haemorrhages, dilation of blood vessels during inflammation, etc. To assess the state of the circulatory system in the stroma of the adrenal glands, we chose the adrenal cortex since the predominant type of vessels in the medulla are veins that do not belong to the microcirculatory channel. In addition, studies show that the main negative effect of venom toxins is on the cortex, not the medulla, so it is more appropriate to analyse the microcirculation there [2].

In order to quantitatively assess the general condition of the adrenal parenchyma cells, we chose to calculate the nuclear-cytoplasmic ratio in the endocrine cells of zona glomerulosa and zona fasciculata because, according to the literature, these two zones are the most vulnerable to the influence of venom toxins. The action of venomous substances on the cell is characterised, on the one hand, by the pyknosis of the nucleus as an early element of the manifestation of necrosis [6]. On the other hand, the cytoplasm is subject to swelling associated with the disruption of the functional activity of mitochondria, which are affected by external factors, in this case, Vipera venom. Karyopyknosis and cytoplasm swelling lead to a decrease in the nuclear-cytoplasmic index.

The results of experimental studies on mice under the administration of Bothrops venezuelensis viper venom showed changes in the qualitative and quantitative composition of the structural components of the adrenal glands. 3 hours after the venom injections, such ultrastructural changes were noted in the animals as the loss of integrity of the endothelial lining of the walls of blood vessels, swelling of mitochondria and disorganisation of their cristae. In the endocrinocytes of the adrenal cortex, the nuclei had indistinct contours with a large amount of heterochromatin and expanded perinuclear spaces [1, 4].

According to Sánchez E. E. and co-authors [22], when the crotamine-like peptide of snake venom of the Crotalidae family affects the cortex of the adrenal glands, zona fasciculata and zona reticularis experience the greatest damage. In the cells of the indicated areas of the adrenal cortex, the expansion of smooth and granular ER was detected during morphological studies, which, according to the researchers, led to a violation of steroid hormone synthesis processes. Vacuolar degeneration, haemorrhages and foci of necrosis were characteristic. In some places, with prolonged exposure to venom toxins, atrophy, nodular hyperplasia and fibroproliferative changes in the cortical substance of the adrenal glands were detected.

The functional activity of the adrenal glands depends on the influence of the central endocrine glands, particularly the pituitary gland. According to the literature, the action of adverse factors, including the viper and snake venom toxins, leads to a violation of the coordinated activity of the pituitary-adrenal system. Experimental studies and data from clinical cases prove the fact that envenomation due to viper bites causes massive haemorrhages in the adrenal and pituitary glands in 36 % and 43 % of cases, respectively. Pathophysiologists are actively studying hemorrhagic necrosis of the pituitary and adrenal glands, but its reliable mechanisms have not yet been elucidated. It was established that the peculiarities of the blood supply of these organs are the cause of the probable extravasation of blood caused by viper toxins. S. Senthilkumaran et al. [27] note that Daboia russelii viper venom contains protein components that have vasculotoxic, hemorrhagic, and proteolytic properties, cause the development of thrombocytopenia, and activate blood coagulation and fibrinolysis factors [21]. The consequence of this is the appearance of consumption coagulopathy and DIC-syndrome. In addition, scientists found a decrease in the blood levels of cortisol, testosterone, ACTH, TTH, and prolactin in the patient's blood, which indicated primary and secondary adrenal insufficiency and damage to the pituitary gland. Attention should be paid to hypotension and circulatory shock, which are the consequences of snake bites and are also associated with disorders of blood supply to vital organs, including the pituitary gland. As a result of a series of autopsies of patients who became victims of snakebites, it was investigated that DIC syndrome is a precursor of haemorrhage or organ necrosis. Some scientists also suggest that dysfunction of the anterior lobe of the pituitary gland may be associated with the formation of autoantibodies. It has been established that acute pituitary insufficiency develops within two weeks with snake and viper bites and is characterised by hypoglycemia and refractory hypotension. Chronic failure can be asymptomatic and characterised by fatigue and weight loss. The researchers note that somatotropocytes (83 %) and gonadotropocytes (50 %) undergo the greatest changes. In the case of the vasotoxic effect of the venom, corticotropocytes are subject to morphological changes (39 %) [25].

Conclusions

1. Administration of *Vipera berus berus* and *Vipera berus nikolskii* venom to rats was accompanied by a significant increase in the area of the microcirculatory bed compared to the control group (in 2.9 times for *Vipera berus berus* and in 6.5 times for *Vipera berus nikolskii*).

2. Exposure to *Vipera berus berus* venom was associated with a significant decrease in the nuclear-cytoplasmic index in rats of the experimental group compared to the control group (13 % and 42 %, respectively), which is evidence of a decrease in the area of the nuclei of endocrinocytes of the adrenal cortex. This index in rats under the conditions of *Vipera berus nikolskii* venom injection was even lower and amounted to 12 %.

3. According to the statistical analysis of the quantitative assessment of the adrenal cortex's state, the similar effect of the venom of both species of vipers at the cellular level is worth noting. At the same time, at the tissue level, the effect of *Vipera berus nikolskii* venom is more pronounced than that of *Vipera berus berus* - this is evidenced by the higher degree of disruption of the structure of the hemomicrocirculatory channel in the adrenal cortex of animals from the group that was affected by this venom. It led not only to an increase in the area of vessels due to their expansion but also to ruptures of their walls and haemorrhages into the surrounding parenchyma and stroma.

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АНАЛІТИЧНА І КІЛЬКІСНА ОЦІНКА СТРУКТУРНИХ КОМПОНЕНТІВ НАДНИРКОВИХ ЗАЛОЗ ЩУРІВ ЗА УМОВ ВПЛИВУ ОТРУТИ ГАДЮК VIPERA BERUS BERUS ТА VIPERA BERUS NIKOLSKII

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Отруєння внаслідок укусів змій є частою, але занедбаною проблемою охорони здоров'я в усьому світі та особливо в тропічних країнах. Щорічна смертність, як наслідок зміїних укусів, перевищує 138 000. Вважають, що дана проблема є недооціненою і в багатьох країнах окремі випадки укусів не підлягають належній фіксації. Метою дослідження є аналітична і кількісна оцінка структурних компонентів надниркових залоз щурів за умов впливу отрути гадюк Vipera berus berus та Vipera berus nikolskii. Експериментальні дослідження проводили на білих нелінійних щурах самцях. Отруту гадюк Vipera berus berus та Vipera berus nikolskii отримували з Харківського національного університету імені В. Н. Каразіна. Люфілізовану нативну отруту зберігали при -20 °C, а потім розчиняли у фізіологічному розчині безпосередньо перед експериментом. Тварин розподіляли на три групи (контрольну і 2 дослідних) по 10 особин у кожній. Дослідним щурам внутрішньоочеревинно вводили напівлетальну дозу (LD50) (1,576 мг/г$^{-1}$) отрути Vipera berus berus або Vipera berus nikolskii на фізіологічному розчині. Тваринам контрольної групи вводили внутрішньоочеревинно лише фізіологічний розчин. Виводили щурів з експерименту через 24 години після впливу отрути, знеживлюючи шляхом цервікальної дислокації. Статистичний аналіз площі мікроцикруляторного русла та ядерно-цитоплазматичного індексу проводили за допомогою програми Fiji: ImageJ та обробляли в Excel. Введення щурам отрути гадюк Vipera berus berus та Vipera berus nikolskii супроводжувалось достовірним збільшенням площі мікроциркуляторного русла відносно групи контролю (в 2,9 рази для Vipera berus berus та в 6,5 разів для Vipera berus nikolskii). Вплив отрути гадюк Vipera berus berus асоціювався зі значним зниженням ядерно-цитоплазматичного індексу у щурів дослідної групи порівняно з групою контролю (13 % та 42 % відповідно), що є свідченням зменшення площі ядер ендокриноцитів кори надниркових залоз. За умови введення щурам отрути гадюк Vipera berus nikolskii цей показник був ще нижчим та становив 12 %. Результати статистичного аналізу кількісної оцінки стану кіркової речовини надниркових залоз показали подібний вплив отрут обох видів змій на клітинному рівні. При цьому на тканинному рівні дія отрути Vipera berus nikolskii проявлялась більш виражено, ніж Vipera berus berus: про це свідчив вищий ступінь порушення структури гемомікроциркуляторного русла у корі надирників тварин у групі, в котрій використовували цю отруту. Дія отрути Vipera berus nikolskii призводила не лише до підвищення площі судин через їх розширення, але й до розриву їх стінок та крововиливів в оточуючі паренхіму і строму.

Ключові слова: *гадюки, отрута, ядерно-цитоплазматичний індекс, мікроциркуляторне русло, щури.*

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