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PHARMACOLOGICAL SCREENING OF A POTENTIALLY EFFECTIVE COMPOUND FOR THE TREATMENT OF CHRONIC TRAUMATIC ENCEPHALOPATHY AMONG NEW PYRIMIDINE DERIVATIVES

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Abstract

The study was performed on male Wistar rats. Pathology modeling was carried out by means of traumatic impact of a load on the parietal region of the skull of animals (weight 150g from a height of 50 cm) for 7 days (one injury per day). On day 8, cognitive and sensorimotor functions were evaluated. The concentration of biochemical parameters (lactate, pyruvic acid, homocysteine) and markers of neurodegradation (glial fibrillar acid protein, protein S-100B, β-amyloid) was also determined in the blood serum. The reference drugs were choline alfoscerate (100 mg / kg) and hopatnenic acid (100 mg/kg). The study found that the use of one of the test new pyrimidine derivatives allowed to achieve a significantly significant normalization of metabolic processes in the form of a decrease in the concentration of lactate and homocysteine by 110.5% ($p<0.001$), 31.3% ($p<0.05$), respectively, and an increase in the content of pyruvic acid by 129.5% ($p<0.05$). The level of glial fibrillar acidic protein, S-100B protein, and beta-amyloid was also reduced by 2.4 times ($p<0.001$), by 198.8% ($p<0.001$), and by 2.2 times ($p<0.001$), respectively. Based on the results of the study, it was established that the new pyrimidine derivative has a cerebroprotective effect in the conditions of experimental chronic traumatic encephalopathy.

Key words: *chronic traumatic encephalopathy, pyrimidine derivatives, cognitive and sensorimotor dysfunctions*

Introduction

According to recent studies, chronic traumatic encephalopathy (CTE) is a progressive neurodegenerative pathology that belongs to a group of diseases characterized by the term "taupathies" [1]. The first reports of CTE in the medical literature were made by *Harrison Martland*, a New Jersey physician in 1928. The scientist described a complex of clinical manifestations in the form of confusion, impaired coordination, slowing down of muscle activity, which he observed during the examination of athletes, boxers who perform in the ring for a long time, subject to repeated concussions of the brain [2]. To date, a greater number of manifestations of this pathology have been established: cognitive dysfunction (decreased memory, mindfulness, dementia), motor disorders (dyskinesia, spasticity, ataxia), behavioral abnormalities (depression, aggression, anxiety) [3, 4]. The main etiological factor in the development of this CTE is probably repeated brain injuries that trigger cascades of neurodegenerative processes [5]. The latter, lead to progressive disorders of the physiological metabolism of the brain, which is expressed in the form of lactate acidosis, hyperhomocysteinemia and reduced pyruvic acid secretion, the formation of markers of neurodegradation, in particular glial-fibrillar acidic protein (GFAP), β-amyloid (Aß), and S-100B protein [6,7]. The above will ultimately contribute to the imminent death of neurons and glia, leading to distortion or loss of a number of brain functions.

The risk group for developing CTE undoubtedly includes athletes engaged in contact sports, the militarists, who are subject to periodic traumatic brain injuries and the effects of explosive waves [8]. However, there is already reliable information about the presence of CTE in persons not involved in sports and army. This is due to the huge number of domestic injuries received in everyday life. Do not forget about road accidents, according to statistics, as a result of the latter, there is a high frequency of concussion in its participants. The above makes the studied pathology more socially significant for the entire population than previously thought [9]. Prevention and treatment of CTE is an important medical and social problem, due to the high mortality and degree of disability among patients, which leads to a decrease in the level and quality of life of patients and people around them.

Materials and methods

Experimental animals

The study was performed on 140 rats (males weighing 240-260g of the *Wistar* line). The animals were obtained from the Rappolovo animal nursery (Leningrad region). The manipulations carried out with the rats strictly complied with the European Convention for the Protection of Vertebrates Used for Experiments and Other Scientific Purposes (Strasbourg, 1986). During the study, the rats were placed in standard vivarium conditions (air temperature 22±2 °C, relative humidity 60±5%, natural change of the daily cycle). The animals were kept in 10 individuals in macrolone boxes (the bedding material is a granular fraction of solid wood (beech)). Access to food and water was not restricted.

Test-objects

In the course of this experimental work, new pyrimidine-4(1H)-one sulfonates synthesized at the Department of Organic Chemistry of the Pyatigorsk Medical and Pharmaceutical Institute were used as test objects. For screening, 10 compounds were selected, under the laboratory ciphers Com-1, Com-2, Com-3, Com-4, Com-5, Com-6, Com-7, Com-8, Com-9, Com-10. The latter were administered orally at a dose of 100 mg / kg, once a day, for 7 days, 30 minutes after modeling the pathology. Choline alfoscerate (Cerepro, Veropharm, RF, 100 mg/kg) [10], hopanthenic acid (Pantogam, PIK-PHARMA PRO, RF, 100 mg/kg) [11] were used as reference drugs according to the above algorithm.

Research design

The animals were divided into 14 groups of 10 individuals each. The first group of rats – the group of positive control/intact (PC), the second – the group of animals of negative control (NC). The third and fourth groups were rats that were injected with reference drugs, choline alfoscerate and hopanthenic acid. In the fifth – fourteenth groups of animals - the test compounds. The design of the study is shown in Figure 1.

Experimental model of CTE

The pathology was reproduced using the device, consisting of a hollow cylinder, a platform for the animal with retainers. After immobilization, the rats were subjected to a mechanical load (weight 150 g)

on the parietal region of the animal's skull from a height of 0.5 m for 7 days (a single exposure per day) [12].

Methods for assessing cognitive functions

Extrapolation Disposal Test (EDT)

The test was performed in an device consisting of a cylindrical container (D=0.35 m, h=0.40 m) filled with water to the level of 0.175 m from the bottom. In the latter, a glass cylinder was fixed in the center (D=0.09 m, h=0.22 m). The lower boundary of the cylinder was submerged in water at 0.025 m. The animal was placed inside the cylinder, tail down, and the behavior of the rats was observed for 2 minutes. The studied indicators were the number of unsuccessful cases of avoidance, manifested in the form of jumps, and the latent period before diving [13].

Test "conditioned reflex of passive avoidance" (CRPA)

The study of cognitive functions was carried out using an device with two compartments, illuminated and dark, in the latter there was an electrode floor. Before performing the main experiment, training was performed by placing the animal on the illuminated part, because of the different behavioral interests of the rats, they moved to the dark part, where the electroshock effect occurred, as a result of which the animals left this compartment. Then, the CRPA preservation was checked by re-placing the animal in a light chamber after a day. The studied parameters were the number of visits to the dark compartment, the latent time of the first approach, and the amount of time that the rats spent in the light and dark parts of the installation for two minutes [14].

Method for evaluating sensorimotor functions

" Beam walking test»

The study of sensorimotor functions of animals was carried out using an installation consisting of a horizontal bar (L=1.65 m), at the end of which a dark camera is fixed. At the beginning of this bar is the "starting" platform. The gap between the platform and the dark chamber (length 1.35 m) is a uniformly narrowing area (from 0.06 m to 0.015 m). Throughout the entire track, at a level of 2 cm below its main plane, on both sides there are protrusions (width 0.02 m), on which the rats place their limbs in case of sensorimotor disorders. Before performing the experiment, the animals were placed in a dark chamber for 60 seconds. The duration of the study of sensorimotor functions is 120 seconds. The estimated indicators were the number of positions on the ledges and the number of positions when the hand and foot are located at both levels, and the total number of steps taken before entering the dark compartment or during the experiment period [15].

Biomaterial sampling and sample preparation

The biomaterial was the brain and blood of animals, the latter was obtained from the basilar arteries and the sagittal venous sinus. Further sample preparation consisted in centrifugation of fresh citrate blood in the 1000g mode, 10 min until the serum, in which the concentration of biochemical parameters and markers of neurodegradation was determined. The rat brain was subjected to homogenization, then centrifugation (PBS 7.2 ratio 1:7, at a speed of 6000 g) in order to obtain a supernatant of the brain tissue in which the determination of Aß was carried out.

Methods for determining the level of biochemical parameters

Method for determining the concentration of lactate and pyruvic acid

The level of lactate and pyruvic acid content was assessed by the enzymatic colorimetric method using a standard set of reagents manufactured by Arbis+ (series: 021).

Methods for assessing the content of homocysteine

The homocysteine concentration was determined using the enzymatic colorimetric method using a standard set of reagents manufactured by DiaSys (series: 021).

Method for assessing the content of neurodegradation biomarkers

The concentration of GFAP, Aß, and S-100B was determined by solid-phase enzyme immunoassay using a species-specific reagent kit manufactured by Cloud Clone Corp. (USA). The course of the analysis is followed to the instructions attached by the manufacturer to the reagents kits.

Methods of statistical analysis

The obtained results were subjected to statistical processing using the STATISTICA 13.0 software package (StatSoft, Inc., USA). The average values and the standard error of the average were set. The obtained data were also analysed using the Shapiro-Wilk test for the normality of the distribution. When these results were subject to the law of normal distribution, parametric methods were used to compare groups of averages - ANOVA with Newman-Keuls post-processing, and in non-compliance, the method of nonparametric statistics (the Craskell-Wallis test) was used [16].

Results

Based on the results of the assessment of the level of cognitive functions in the TEI test, it was found that in the animals of the PC group, the period before "diving" was equal to 17.8 seconds. At the same time, in rats of the NC group, this time interval increased by 134.8% ($p<0.05$) compared to animals of the PC group. In the groups of rats injected with choline alfoscerate and hopanthenic acid, the studied index decreased by 70.6% ($p<0.01$) and 68.3% ($p<0.05$), respectively, compared to the group of NC rats (Fig. 2).

The use of Com3, Com1, Com9, and Com8 compounds contributed to a reduction in the time period before "diving" relative to the indicator of the NC group of animals by 142.7% ($p<0.05$), 63.3% ($p<0.05$), 46.6% ($p<0.05$), and 26.2% ($p<0.05$), respectively. Against the background of the adminstration of substances under the laboratory ciphers Com2, Com5, Com6, Com4, Com7, Com10, it was noted that the time of "avoidance" did not significantly differ from the values of the NC group of animals (Fig. 2).

During the assessment of the state of cognitive functions using the CRPA test, it was found that in the rats of the PC group, the time period of latent entry into the dark compartment was 32 seconds (Fig. 3). At the same time, in the group of NC animals, the studied indicator decreased by 66.9% ($p<0.05$) compared to the rats of the PC group. Against the background of the administration of reference drugs to animals, choline alfoscerate and hopanthenic acid, there was an increase in the time before entering the dark compartment by 183.3% ($p<0.05$), 2.8 times ($p<0.01$), respectively, compared with the rats of the NC group. When using the Com1 compound in animals, it was found that the rats of this group did not enter the dark compartment. The administratiom of substances under the codes Com8, Com6, Com2 led to an increase in the time of latent entry into the dark compartment by 5.1 times ($p<0.05$), 2.2 times ($p<0.05$), by 84.9% ($p<0.05$) relative to the same indicator of animals of the NC group (Fig. 3). The use of Com4 and Com10 compounds allowed to delay the time to entry in comparison with rats of the NC group by 66.1% ($p<0.05$) and 55.7% ($p<0.05$), respectively. However, the administration of substances Com3, Com5, Com7, Com9 did not contribute to a significant change in the studied indicator relative to the group of NC animals.

Based on the results of the assessment of the level of sensorimotor functions in the studied groups of rats, it was found that in the animals of the PC group, the value of sensorimotor deficit was 10±0.253% (Fig. 4). At the same time, in the NC group of rats, the studied indicator increased by 4.8 times ($p<0.05$) compared to the animals of the PC group. Against the background of the use of choline alfoscerate, a decrease in the level of sensorimotor deficit relative to the group of NC rats was found by 131.4% ($p<0.05$). At the same time, the administration of hopanthenic acid did not contribute to a significantly significant change in the studied indicator in relation to animals of the NC group. The use of Com2 and Com1 test-objects in animals led to a decrease in the level of sensorimotor deficit by 67.1% ($p<0.05$), by 34.9% ($p<0.05$), respectively, compared with the rats of the NC group. At the same time, when the substances Com9, Com3, Com10, Com5, Com6, Com8, Com7, Com4 were administered, there was no significantly significant change in the studied indicator relative to the group of NC animals (Fig. 4).

During the assessment of the level of metabolic processes of the brain, the following was revealed: the concentration of lactate in the rats of the PK group was 1.01±0.083 mmol/l (Fig. 5). At the same time, in the group of NC animals, an increase in the content of the studied indicator relative to the rats of the PC group was 3.4 times ($p<0.05$). The administration of the reference drugs, choline alfoscerate and hopanthenic acid, contributed to a decrease in lactate secretion by 74.7% ($p<0.05$) and

56.2% (p<0.001), respectively, compared with the group of NC rats. When using Com1, Com3, and Com10 substances, the level of lactate content decreased by 110.5% (p<0.001), 62.5% (p<0.01), and 61.3% (p<0.02), respectively, relative to the group of NC animals (Fig. 5). Against the background of administration of Com6 and Com2 compounds to rats, a decrease in lactate concentration was observed by 57.9% (p<0.001) and 52.4% (p<0.01), respectively, in relation to the group of NC animals. Also, when using Com4, Com8, the content of the studied indicator decreased by 47.4% (p<0.02) and 44.4% (p<0.01) compared to the NC group rats. At the same time, the introduction of Com9, Com5, Com7 contributed to a decrease in the lactate concentration by 40.3% (p<0.01), 29.1% (p<0.05), and 25.9% (p<0.02), respectively, relative to the group of NC animals (Fig. 5).

Based on the assessment of the pyruvic acid content in the studied groups of rats, it was found that in the animals of the PC group its value was 100.85±1,165 μmol/l (Fig. 6).At the same time, in the NC group of rats, the concentration of pyruvic acid relative to the animals of the PC group decreased by 3.9 times (p<0.05). When choline alfoscerate and hopanthenic acid were administered, an increase in the level of pyruvic acid was observed by 73.1% (p<0.02), 132.6% (p<0.01) in relation to rats of the NC group (Fig. 6) respectively. The use of Com3, Com9, and Com1 compounds in animals allowed for an increase in the concentration of the studied indicator in comparison with the group of NC rats by 5.2 times (p<0.05), by 2 times (p<0.001), and by 129.5% (p<0.05), respectively. The administration of Com6, Com8, Com7, Com2 increased the content of pyruvic acid by 102.4% (p<0.05), 83.7% (p<0.05), 71.9% (p<0.05), and 31.1% (p<0.05), respectively, relative to the value of the animals of the NC group. At the same time, the use of Com10, Com4, and Com5 compounds did not lead to a significantly significant change in the concentration of pyruvic acid compared to the same indicator in the NC group of animals (Fig. 6).

During the assessment of the homocysteine content, it was found that the value of the latter in the PC group of rats was 10.34±0.59 ng / ml (Fig. 7). At the same time, in the NC group of animals, the concentration of the studied parameter increased by 3.1 times (p<0.05) relative to the PC group of rats. Against the background of the administration of reference drugs, choline alfoscerate and hopanthenic acid, there was a decrease in the content of homocysteine compared to the group of NC rats by 87.5 % (p<0.05), by 2.9 times (p<0.05). The use of Com8, Com5, and Com4 compounds in animals made it possible to reduce the concentration of the studied indicator by 12.5 times (p<0.001), 10.6 times (p<0.001), and 6.7 times (p<0.001), respectively, in relation to rats of the NC group (Fig. 7). When Com10, Com6, and Com3 were administered, homocysteine concentrations decreased 6.5 times (p<0.05), 5.8 times (p<0.001), and 3.7 times (p<0.01) in comparison with the NC rat group. Also, the use of compounds under the laboratory ciphers Com2, Com9, Com7, Com1 allowed to achieve a decrease in the level of homocysteine by 191% (p<0.01), 167.9% (p<0.05), 88.2% (p<0.05), 31.3% (p<0.05), respectively, relative to the animals of the NC group (Fig. 7).

After studying the dynamics of changes of the GFAP concentration, it was found that in the animals of the PC group its value was at the level of 312.27±11.320 pg / ml (Fig. 8). At the same time, the content of the studied indicator in the rats of the NC group increased 7 times (p<0.001) relative to the rats of the PC group. Against the background of the administration of choline alfoscerate and hopanthenic acid, a significant decrease of the GFAP concentration by 2.2 times (p<0.001) and by 139.3% (p<0.02) was found. When used in rats Com3, Com1, Com5, a decrease in the concentration of the studied protein was found by 2.5 times (p<0.001), 2.4 times (p<0.001), and 2.3 times (p<0.001), respectively, relative to the group of NC animals (Fig. 8). The administration of Com7, Com2, and Com10 substances reduced the GFAP content by 2.2 times (p<0.001), 173.6% (p<0.01), and 159.3% (p<0.001), respectively, compared to the animals of the NC group. When using Com8, Com6, Com4, and Com9 compounds in rats, a decrease in the concentration of the studied protein was observed by 147.1% (p<0.001), 139.9% (p<0.05), 133.2% (p<0.01), and 115.9% (p<0.05) relative to the group of NC animals (Fig.8).

When evaluating the Aß content, its value at 12.64±0.501 pg/ml in the PC group of rats (Fig. 9) was found. At the same time, the concentration of the indicator in the NC group of animals increased

by 24.3 times (p<0.001) in relation to the PC group of rats. The administratioon of the reference drugs choline alfoscerate and hopanthenic acid allowed to reduce the content of Aß in comparison to the animals of the NC group by 3.2 times (p<0.01), by 3.7 times (p<0.01), respectively (Fig. 9). When using the studied compounds in rats under the laboratory ciphers Com1, Com2, Com3, there was a decrease in the concentration of Aß by 2.2 times (p<0.001), 2.1 times (p<0.01), and 148.4% (p<0.01), respectively. Against the background of the administration of Com9, Com4, Com7, a decrease in the content of Aß was found in comparison with the rats of the NC group by 145.3% (p<0.01), 136.6% (p<0.02), and 114.8% (p<0.05), respectively. When using Com5, Com6, Com10, Com8, a decrease in the level of Aß was observed by 104.9% (p<0.02), 71.1% (p<0.02), 50.5% (p<0.05), 39.5% (p<0.05) in relation to the group of NC animals (Fig. 9). The value of the c-100B level, according to the results of the study, in the animals of the PC group was 12.92±0.445 pg / ml (Fig. 10). At the same time, in the NC group of rats, the content of this indicator increased by 28 times compared to the animals of the PC group (p<0.001). The administration n of reference drugs choline alfoscerate and hopanthenic acid contributed to a decrease in the concentration of S-100B by 152.8% (p < 0.01), 181.9% (p < 0.01) in relation to the group of NC animals. When using port com4, Com1, and Com5 compounds in rats, the level of c-100B decreased by 2 times (P<0.001), by 198.8% (P<0.001), and by 194.6% (P<0.001), respectively, compared to animals of the NC group. At the same time, the administration of Com7, Com6, Com8, Com9 contributed to a decrease in the concentration of S-100B by 192% (p < 0.001), 155.4% (p < 0.001), 143.9% (p < 0.01), 139.1% (p < 0.001), respectively, in relation to the group of NC rats. When using Com2, Com3, and Com10 compounds, there was a decrease in the content of S-100B relative to animals of the NC group by 128.7% (p < 0.001), 127% (p < 0.001), and 117% (p < 0.001), respectively (Fig. 10).

Discussion

The risk of developing CTE in the population of all ages and professions is currently quite high. This fact is a serious medical and social problem, since according to the results of statistical studies, the susceptibility to TBI and, accordingly, the probability of developing CTE is observed in people of the most able-bodied age of 25-50 years [17]. The progression of CTE inevitably leads to disability, and often to death, thereby reducing the quality of life of patients and people around them. Considering the pathogenesis of the studied pathology, two types of neurodegenerative processes can be distinguished [18]. The first, irreversible, are directly related to the traumatic impact, in which energy is transferred from the translational factor to the brain, thereby generating an increase in pressure and shear forces, leading to deformation and complete destruction of extended structures, axons of neurons and blood vessels [19]. The second, reversible, which develop as a result of the first neurodegenerative processes and are expressed in the form of ischemia and hemorrhages, metabolic disorders, mitochondrial dysfunctions, oxidative stress, activation of apoptotic and necrotic cascades of reactions [20 - 22]. These phenomena lead to the imminent death of neurons and glia, which in turn is expressed by the formation of specific markers of neurodegradation, in particular GFAP, the level of which can be used to judge the degree of brain damage [23].

To date, the number of effective and safe methods of treating CTE is quite limited, which creates prerequisites for the search and development of new therapies [24]. The most promising direction is the screening of compounds with metabolic activity, which will allow to neutralize the secondary cascades of neurodegenerative reactions, which ultimately lead to the activation of apoptotic and necrotic signals. Based on the analysis of literature sources, we put forward the following hypothesis: the use of new pyrimidine derivatives will correct the progression of CTE due to the normalization of metabolic processes, which in turn will be expressed by a decrease in the amount of the neurodegradation biomarker, and as a result, the preservation of cognitive and sensorimotor functions of animals [25]. The criterion for selecting a class of compounds for screening was the previously established cerebroprotective activity of pyrimidines in experimental TBI [26]. Based on the results of the study, it was found that new pyrimidine derivatives contribute to the preservation of the physiological level of metabolic

processes in the rat brain under experimental CTE. Among the 10 substances studied, the compound under the code Com1 has the most pronounced total metabolic activity. The latter was expressed in a significant decrease in the lactate concentration This action exceeds the strength of the pharmacological effect of choline alfoscerate by 20.5% ($p<0.01$). The described evidence indicates a decrease in the level of acidosis in brain cells, as well as energy deficiency, which triggers a cascade of metabolic changes, which in turn lead to necrotic death of brain cells in the conditions of CTE [27, 28]. Also, a decrease in the concentration of homocysteine relative to the rats of the NC group by 31.3% ($p<0.05$) was found, which does not significantly differ from the effect when choline alfoscerate was administered to animals. This manifestation eliminates the direct damaging effect of homocysteine on the endothelium, due to a decrease in its content, there is also an increase in nitric oxide production, a modulation of sensitivity to it, and a decrease in the intensity of atherosclerotic processes [29,30]. The above indicates that the use of Com1 probably contributes to slowing the progression of neurodegradation, and is expressed by a reduction in the concentration of neurodegradation biomarkers GFAP, Aß, S-100B. As a result of the normalization of metabolic processes and reduction of the destruction of brain cells on the background of the administration of Com1, the preservation of the cognitive functions of rats in experimental CTE was found. Thus, using the TEI test, a decrease in the time period for completing the task was found by 63.3% ($p<0.05$) relative to the animals of the NC group. The preservation of a memorable trace in the CRPA test was also revealed, the latter was expressed by the fact that the rats receiving Com1 did not enter the dark compartment, where they were previously exposed to electroshock irritation.

Conclusions

Based on the results of a screening study aimed at finding a compound for the effective treatment of CTE, it follows that among the 10 new pyrimidine derivatives, the most pronounced pharmacological effect is the substance Com1. The mechanism of action probably consists in maintaining the physiological level of metabolism, reducing the degree of neurodegradation. The latter manifests itself in the form of preservation of cognitive and sensorimotor functions of animals, which makes it promising to further study Com1 as a means of CTE therapy.

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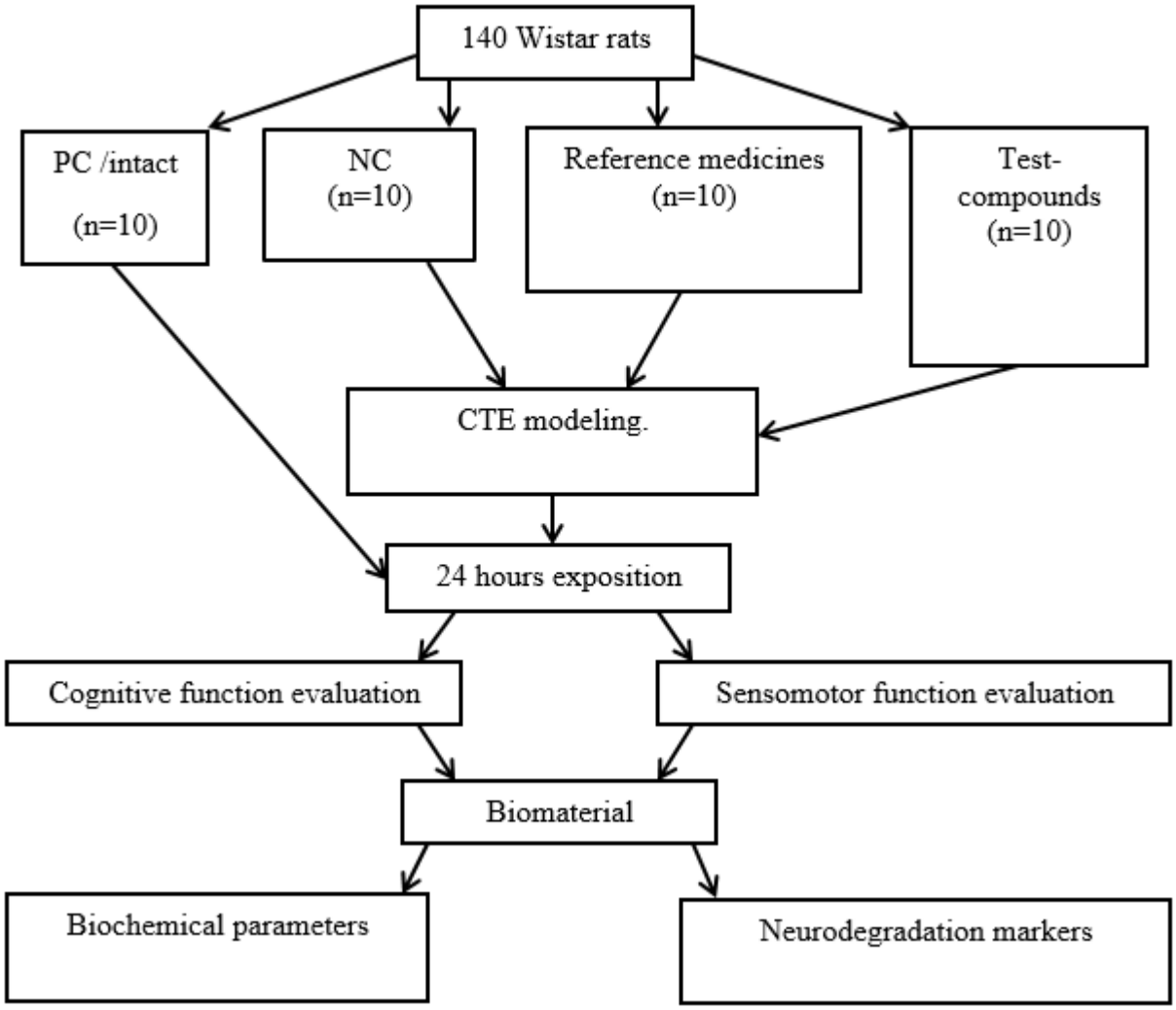
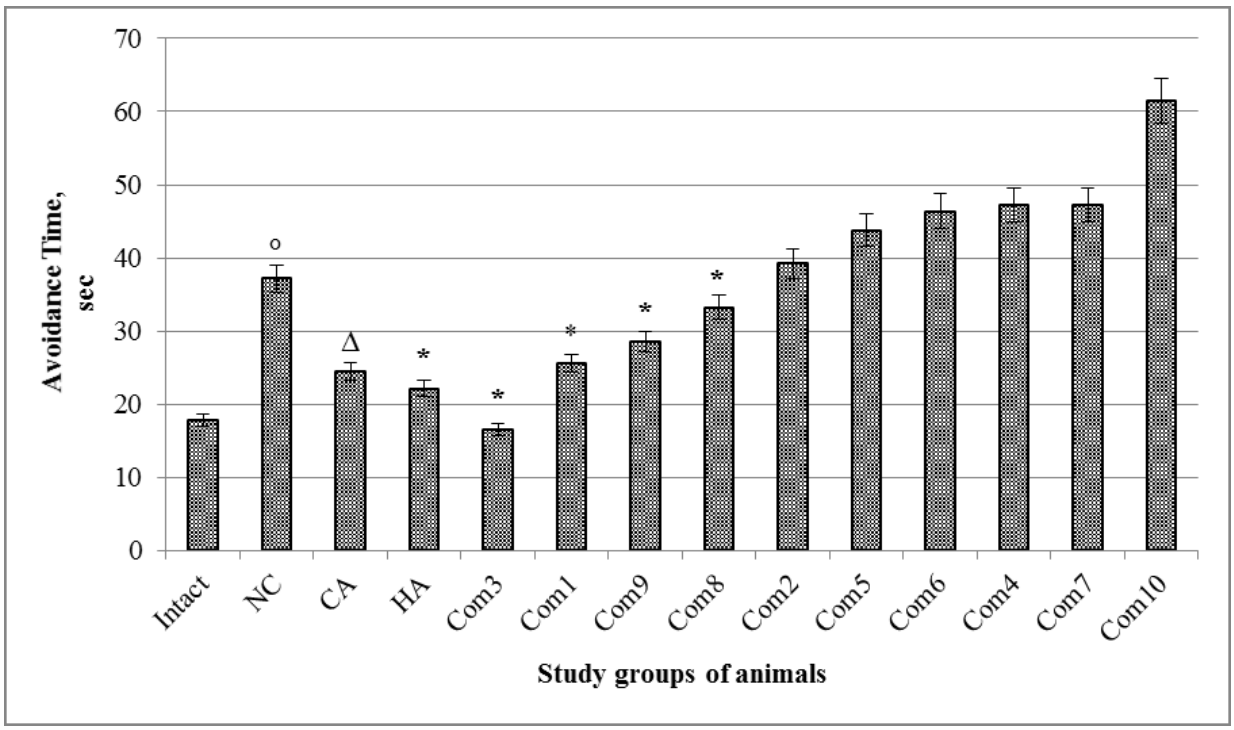
Figures



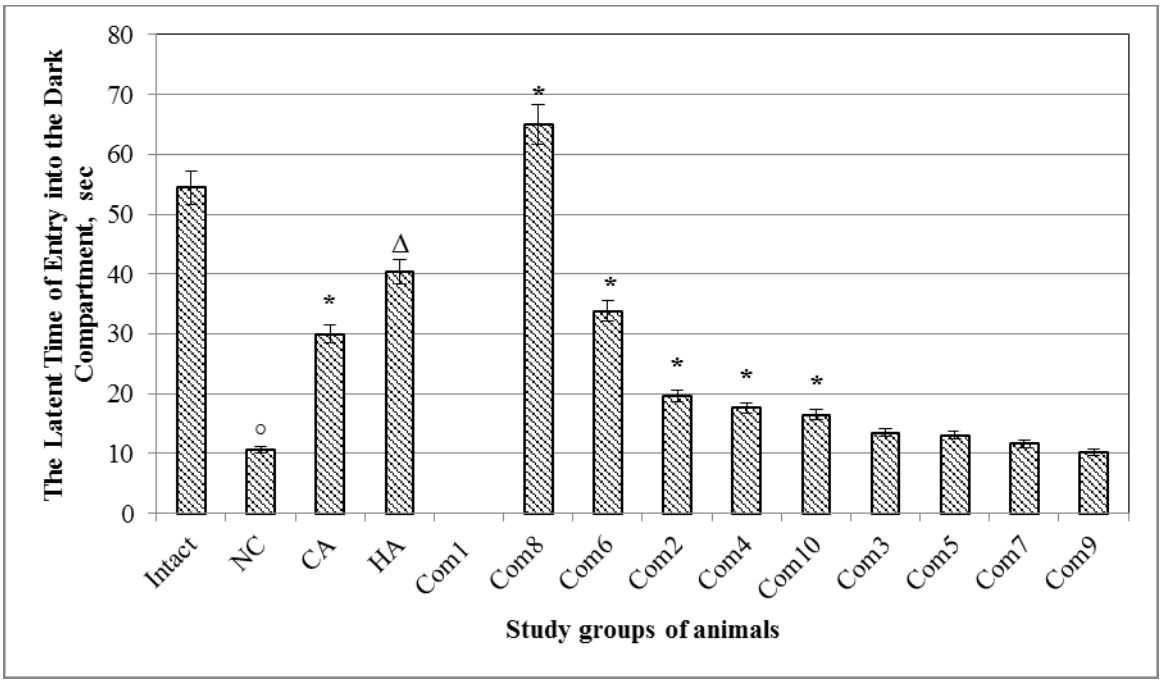
Note: PC is a group of positive control rats, NC is a group of negative control animals.

Figure 1. Study design



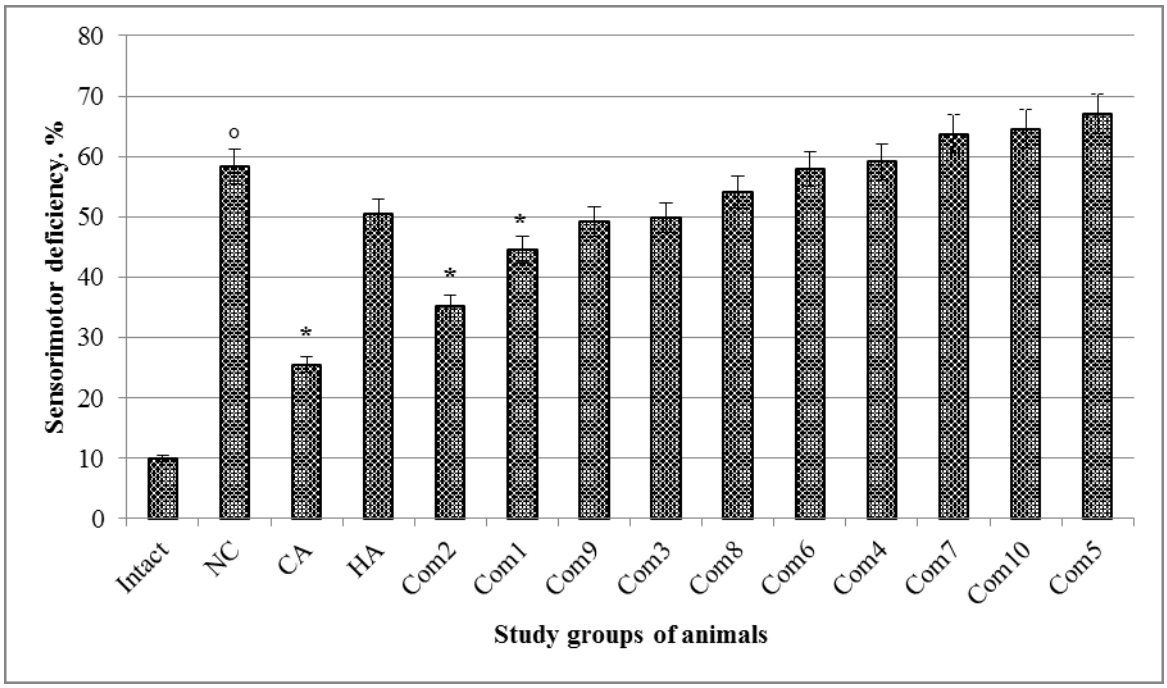
Note: statistically significant (Newman-Keuls test) relative to the PC group of animals (°- p<0.05), relative to the NC group of rats (*- p<0.05; # - p<0.001; Δ - p<0.01).

Figure 2. Determination of the level of cognitive functions of rats in the TEI test under experimental CTE and its correction



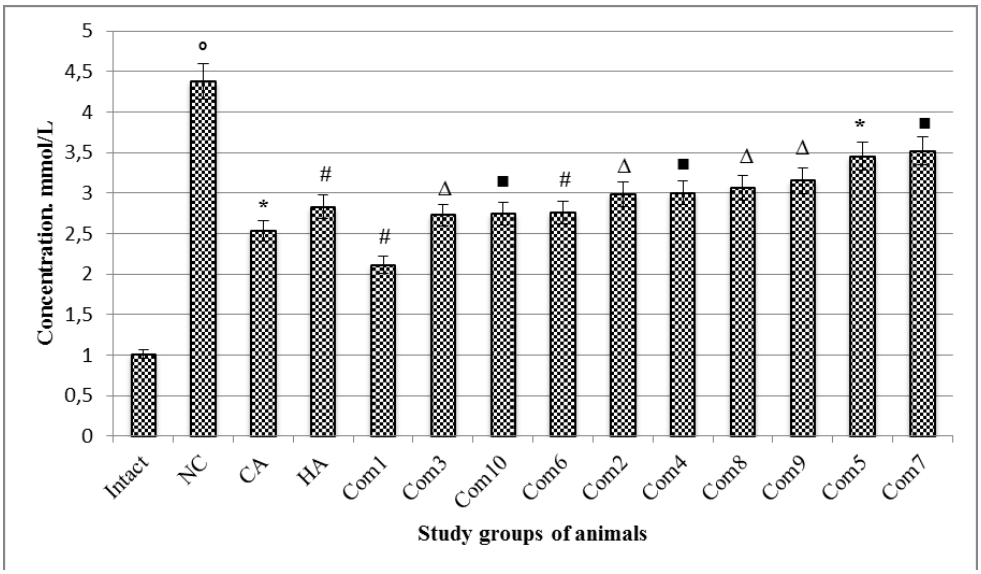
Note: statistically significant (Newman-Keuls test test) relative to the PC group of animals (°- p<0.05), relative to the NC group of rats (*- p<0.05; # - p<0.001; Δ - p<0.01).

Figure 3-Assessment of the state of cognitive functions of rats in the CRPA test under experimental CTE and its correction



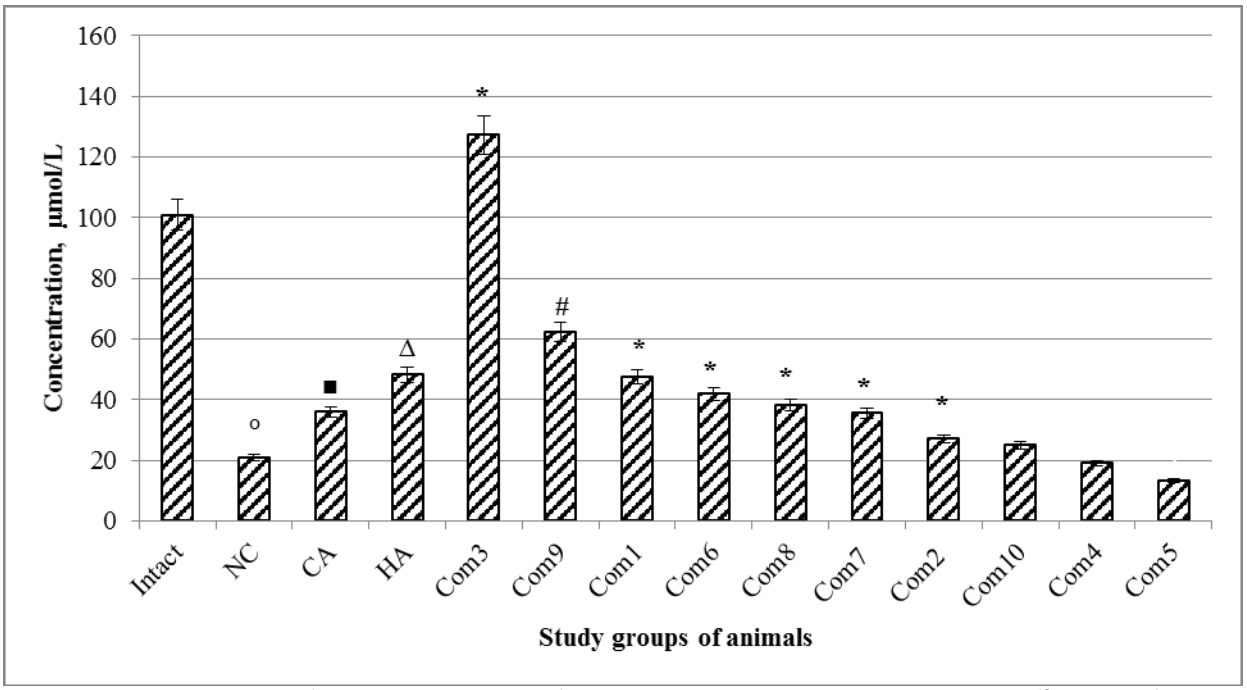
Note: statistically significant (Newman- Newman-Keuls test) relative to the PC group of animals (°- p<0.05), relative to the NC group of rats (*- p<0.05; # - p<0.001; Δ - p<0.01).

Figure 4. Changes in the values of sensorimotor deficits in the studied groups of rats under the conditions of experimental CTE and its correction



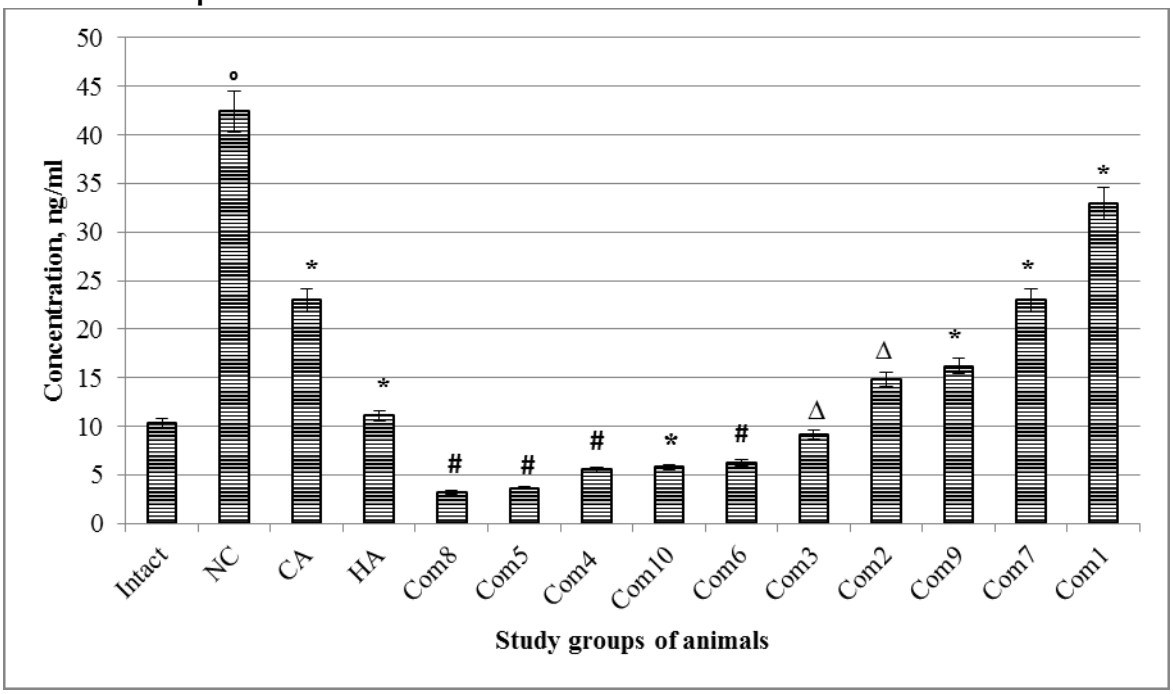
Note: statistically significant (Newman-Keuls test) relative to the PC group of animals (°- p<0.05), relative to the NC group of rats (*- p<0.05; # - p<0.001; Δ - p<0.01, ■ - p<0.02).

Figure 5-Study of the dynamics of changes in the content of lactate in the blood serum of the studied groups of animals under the conditions of experimental CTE and its correction



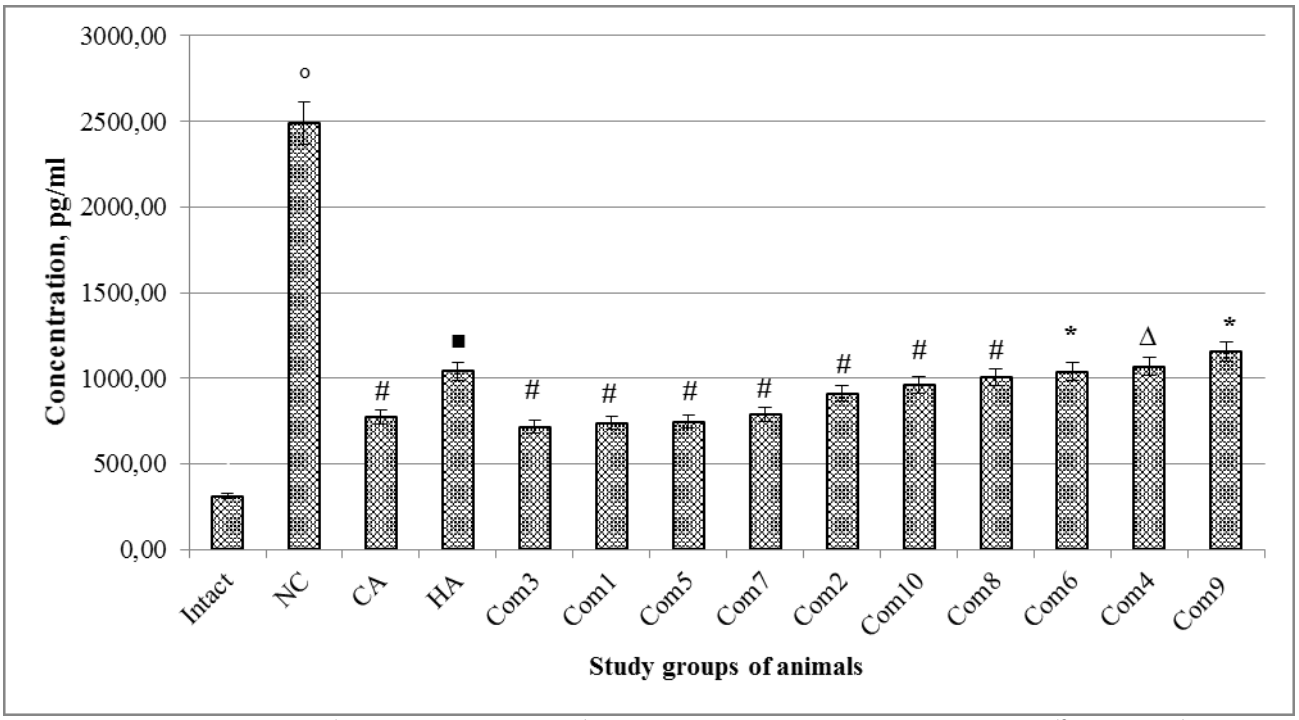
Note: statistically significant (Newman-Keuls test) relative to the PC group of animals (°- p<0.05), relative to the NC group of rats (*- p<0.05; # - p<0.001; Δ - p<0.01, ■ - p<0.02).

Figure 6-Changes in the concentration of pyruvic acid in the blood serum of the studied groups of animals under the conditions of experimental CTE and its correction



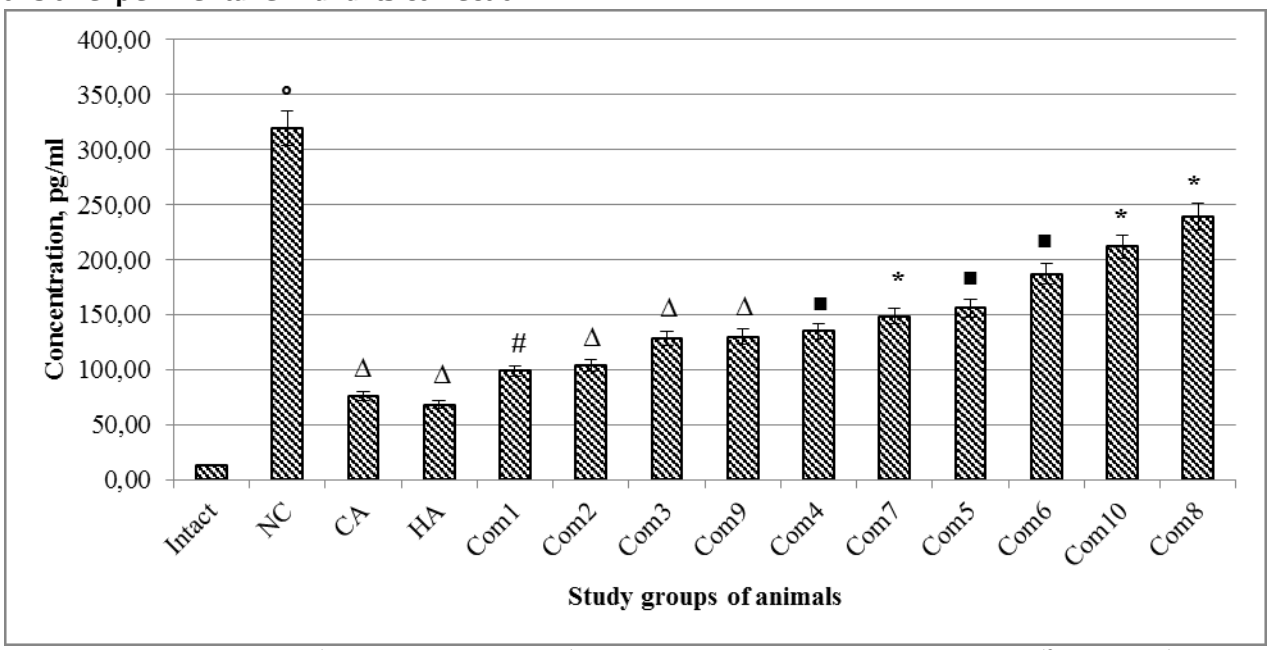
Note: statistically significant (Newman-Keuls test) relative to the PC group of animals (°- p<0.05), relative to the NC group of rats (*- p<0.05; # - p<0.001; Δ - p<0.01, ■ - p<0.02).

Figure 7-Changes in the concentration of homocysteine in the blood serum of the studied groups of animals under the conditions of experimental CTE and its correction



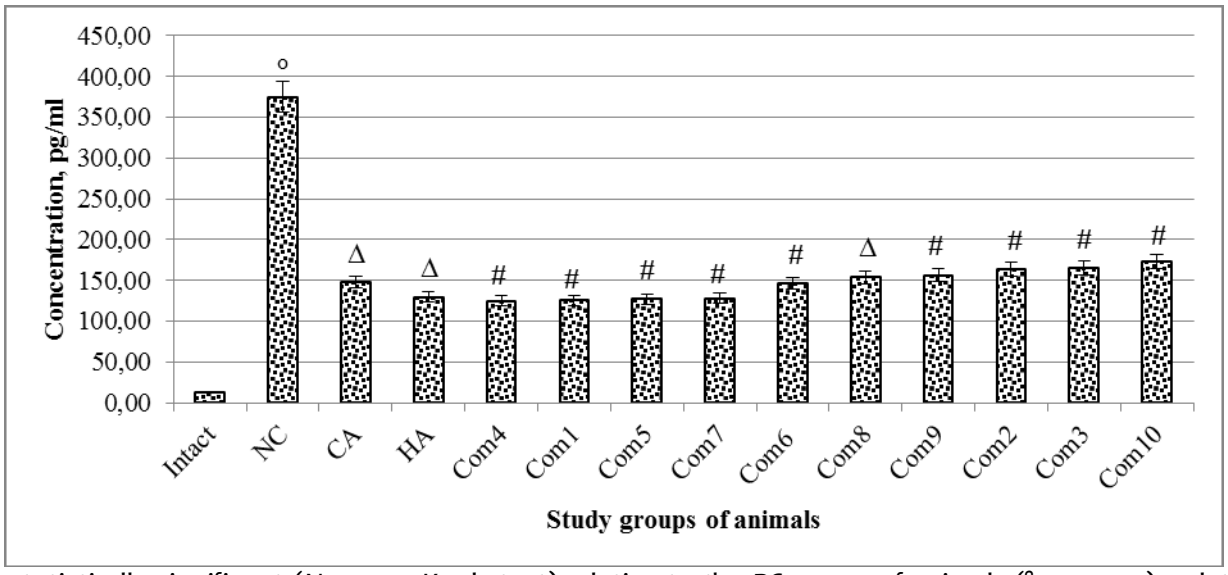
Note: statistically significant (Newman-Keuls test) relative to the PC group of animals (°- p<0.001), relative to the NC group of rats (*- p<0.05; # - p<0.001; Δ - p<0.01, ■ - p<0.02).

Figure 8-Changes in the concentration of GFAP in the blood serum of the studied groups of animals under the conditions of experimental CTE and its correction



Note: statistically significant (Newman-Keuls test) relative to the PC group of animals (°- p<0.001), relative to the NC group of rats (*- p<0.05; # - p<0.001; Δ - p<0.01, ■ - p<0.02).

Figure 9. Assessment of the dynamics of changes in the level of Aß in the brain tissue supernatant in the studied groups of animals under the conditions of experimental CTE and its correction



Note: statistically significant (Newman-Keuls test) relative to the PC group of animals (°- p<0.001), relative to the NC group of rats (*- p<0.05; # - p<0.001; Δ - p<0.01, ■ - p<0.02).

Figure 10. Evaluation of changes in the content of S-100B in the blood serum of the studied groups of animals under experimental CTE and its correction