ORIGINAL RESEARCH/ОРИГІНАЛЬНІ ДОСЛІДЖЕННЯ

DEVELOPMENT OF PATHOLOGICAL CHANGES IN THE ORAL CAVITY ORGANS OF ANIMALS UNDER CONDITIONS OF POLYNEUROPATHIES OF DIFFERENT GENESIS

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The aim of our research is to study the effect of polyneuropathy of different genesis on the development of pathological changes in the large salivary glands and periodontal tissues of animals.

Methods. The study was conducted on 62 laboratory rats of both sexes. Toxic polyneuropathy was induced by paclitaxel injection, experimental type 1 diabetes mellitus was modeled by streptozocin injection, and alcoholic polyneuropathy was induced by chronic administration of increasing concentrations of ethanol. The development of polyneuropathy was confirmed by a change in the pain sensitivity threshold (PST) using the Randall-Selitto tensoalgometric method. In the homogenate of oral cavity organs, total proteolytic and total antitryptic activity, catalase activity, content of TBARS, average mass molecules, oxidatively modified proteins, fucose and glycosaminoglycans (GAG), and amylase activity were determined. The level of total, protein-bound and non-protein sulfhydryl groups, activity of superoxide dismutase, glutathione peroxidase, glutathione transferase, glutathione reductase; content of reduced and oxidized glutathione, diene conjugates and Schiff bases were determined in blood serum.

Results. We established the increasing of PST in animals that were simulated neuropathies of different genesis. All three types of polyneuropathies are accompanied by the development of carbonyl-oxidative stress in the soft tissues of the periodontium and large salivary glands of rats, which is evidenced by a probable increase in the content of oxidatively modified proteins and the content of TBARS, as well as average mass molecules compared to these indicators in intact animals. Under the conditions of modeling all three polyneuropathies, the protein-synthetic activity in the large salivary glands is suppressed, as evidenced by a decrease in the activity of α-amylase. Under conditions of experimental diabetic and toxic neuropathy in the salivary glands of animals, changes in the proteinase-inhibitor balance of the compensatory type are observed. We found that polyneuropathies of different genesis cause increased catabolism of biopolymers of the extracellular matrix of the periodontal connective tissue of rats, which confirms the increase in the content of GAG and fucose compared to these indicators in control animals.

Conclusions. Under conditions of diabetic, toxic and alcoholic neuropathy, the amylolytic activity of the large salivary glands of animals is suppressed, the balance of the pro- and antioxidant system changes. When modeling peripheral polyneuropathy in animals by administration of paclitaxel,
Polyneuropathies are generalized disorders of the peripheral nervous system of multifactorial etiology with variable and diverse manifestations [1]. Peripheral polyneuropathies are especially common as a complication of diabetes mellitus, ethyl toxicity and neurotoxicity in the setting of cancer chemotherapy; the first two causes are responsible for 75% of all polyneuropathies.

Diabetes mellitus (DM) remains a medical and social problem in almost all countries of the world. The prevalence of diabetes in industrialized countries is 6-7% and tends to increase. Previously, 3 million people were said to be added to the number of people with diabetes annually, but today this figure reaches 5.5 million. This is mainly due to the growth of the number of people with type 2 diabetes. Estimates show that if the average life expectancy increases to 80 years, the number of patients with type 2 diabetes will increase to 18% of the total population. The great social significance of diabetes is that it leads to early disability and mortality due to the presence of vascular complications of diabetes: microangiopathy (retinopathy and nephropathy), macroangiopathy (myocardial infarction, stroke, lower limb gangrene), and neuropathy.

Although the pathogenesis of late complications of diabetes is complex, chronic hyperglycemia or lack of diabetes compensation plays a major role in their initiation and progression. This has been reliably confirmed by studies by the American Diabetes Association, which has shown that strict compensation allows for primary prevention of retinopathy by 76%, secondary prevention of retinopathy by 54%, clinical neuropathy by 60%, reduction of microalbuminuria by 39% and albuminuria by 54%. At the same time, the development of diabetic polyneuropathy is based on damage to the longest sensory axons, so the frequency of polyneuropathy depends on the method used to diagnose nervous system lesions. Thus, when using electrophysiological methods of research and myography, the incidence of peripheral nerve damage increases to 70-90%.

The prevalence of diabetic neuropathy in newly diagnosed patients with diabetes mellitus is 8%, reaching more than 50% in those with a long history of the disease [2]. Diabetic neuropathy is one of the most common complications of diabetes mellitus, affecting mainly sensory and autonomic axons, and gradually, to a lesser extent, motor axons. Initially, the longest sensory axons are damaged, so the manifestations are initially distal, developing to the proximal ones. Gastrointestinal autonomic neuropathy is usually a diagnosis of exclusion due to the difficulty of assessing gastrointestinal function in humans. It affects up to 75% of people with DM [3]. There are various forms of manifestation of DM, with the most common form being generalized symmetric polyneuropathy with distal onset.

Due to the increasing prevalence of malignant diseases and the use of new chemotherapeutic agents, chemotherapy-induced neuropathies have gained clinical importance; their prevalence is 30-40%, with wide variations depending on the drug and treatment regimen used. Neurotoxicity is one of the specific systemic complications of chemotherapy, which affects both the quality of life of cancer patients and the ability to provide life-saving anticancer treatment [4]. Neurotoxicity depends on the individual dose, the cumulative total dose, and the duration of chemotherapy. Peripheral polyneuropathy is the most common manifestation of neurotoxicity. Chemotherapy-induced polyneuropathy is based on damage to the peripheral motor, sensory and autonomic neurons, which is clinically manifested by various sensory (paresthesias, numbness, pain), motor (muscle weakness, paresis), autonomic (gastrointestinal motility disorders, arrhythmias) disorders, as well as the development of neuropathic pain. Paclitaxel is widely used to treat common cancers such as breast, ovarian, lung, and other cancers. Taxanes, namely paclitaxel, are diterpene alkaloids that bind and help stabilize microtubule polymerization by interacting with a specific site on β-tubulin [5], which
prevents microtubule depolymerization and induces apoptosis in proliferating cells by stabilizing the mitotic spindle. As a result, the inability of the cell to deconstruct the mitotic spindle during mitosis leads to cell cycle termination with arrest in the G2/M phase [6]. A meta-analysis showed that paclitaxel-induced peripheral polyneuropathy affects 44% to 98% of patients [7]. The leading mechanisms responsible for the development of chemotherapy-induced peripheral neuropathy are mitochondrial dysfunction, oxidative stress, DNA damage, impaired axonal transport, and ion channel remodeling in peripheral nerves [8].

According to various authors, alcohol-related polyneuropathy develops in 13-30% of people suffering from alcohol dependence, leading to permanent disability. At the same time, latent asymptomatic forms of alcohol-related polyneuropathy are detected in 97 - 100% of patients with chronic alcohol abuse during a comprehensive examination. Alcohol abuse is known to cause a number of neurological disorders, including cerebellar ataxia, confusion, cognitive impairment, and peripheral neuropathy. Neuropathies associated with chronic alcohol abuse can involve large and/or small (including autonomic) fibers and are quite heterogeneous in their clinical and pathological features [9]. The pathogenesis of alcohol-related polyneuropathy is not fully understood to date. The leading mechanisms of alcohol-related polyneuropathy are discussed: B vitamin deficiency associated with malnutrition and/or malabsorption syndrome; direct toxic effects of ethanol and its biotransformation metabolites; trafficking of microbiota from the gut and activation of Kupffer cells, which stimulates NF-κB-induced inflammation; induction of mir-9 expression, which leads to lipid metabolism disorders, inhibition of the glutathione system, endoplasmic reticulum stress, and activation of free radical oxidation [10, 11]. The neurodepressive effect of ethanol occurs due to the blockade of the NMDA receptor, which counteracts the excitatory effect of glutamate, and ethanol withdrawal leads to excitotoxicity due to stimulation of NMDA receptors [12].

The aim of this paper is to study the effect of polyneuropathies of different genesis on the development of pathological changes in the organs of the rat oral cavity, in particular, the major salivary glands and periodontal tissues.

Materials and methods

Experimental studies were conducted at the scientific laboratory of the Department of Biological and Bioorganic Chemistry of Poltava State Medical University and the research laboratory of the Educational and Scientific Center "Institute of Biology and Medicine" of Taras Shevchenko National University of Kyiv. When working with animals, the requirements of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 20.09.1985), the basic rules of good laboratory practice GLP (1981), the Law of Ukraine № 3447-IV of 21.02.2006 "On the Protection of Animals from Cruelty" were followed [13].

Animals 62 laboratory rats of both sexes aged 150 days, which were selected for modeling neuropathies, after one week of aclimatization were randomly divided into 4 groups: group 1. intact, group 2. paclitaxel-induced neuropathy, group 3. streptozocin-induced diabetic neuropathy, group 4. alcoholic neuropathy and were kept in a vivarium in accordance with the rules of zoohygiene and maintaining a 12/12 hour daily light-dark cycle with constant aeration, air temperature (26°C) and humidity (43±2%) of the internal environment on a mixed grain and vegetable diet and water, which were received ad libitum.

Modeling of toxic neuropathy. Toxic polyneuropathy in rats was induced by intraperitoneal injection of paclitaxel (Actavis Italy; 100mg/16.7ml, 5GN5122 series) at a dose of 2 mg/kg on days 0, 2, 4, and 7 [14]. Before the first injection, the rats were numbered and weighed, and pain sensitivity was assessed by applying mechanical stress with increasing pressure: an initial pressure of 20 g/cm² was applied to both hind legs of the rat using an analgesimeter according to the Randall-Selitto method. Such measurements allow us to determine baseline values before the development of neuropathy. The increase in the nociceptive threshold, which corresponds to the degree of neuropathy, is maximal between days 16 and 24 after the first injection of paclitaxel.

Modeling of diabetic neuropathy. Experimental type 1 diabetes mellitus was modeled in rats according to Islam S. and Choi H. [15]. Experimental mature rats weighing 180-200 g were injected with streptozocin (Streptozocin, Sigma, USA) intraperitoneally - 65 mg/kg. To confirm the presence of diabetes mellitus, blood glucose levels were measured in rats on days 14 and 28 of the experiment before modeling the pathology. The glucose concentration was measured using a Free Style Optium XEMV036-P0270 glucose meter and a Free Style Optium H test strip. The presence of diabetic polyneuropathy was confirmed using an analgesimeter. On day 30 of the study, a glucose tolerance test was performed to confirm the development of diabetes mellitus in rats. The initial glucose level was determined on an empty stomach, after which the rats were intragastrically injected with a glucose solution at a dose of 3 g/kg. After 30, 60, 90 and 120 min after glucose administration, its concentration in the blood was measured. Based on the test results, a hyperglyce-
mic curve was constructed, which corresponded to
the diabetogenic curve.

Modeling of alcoholic neuropathy. Alcoholization of
erats was carried out according to the following
scheme: animals were injected endogastrically with
ethanol of different concentrations using a probe for
72 days: 1-24 days - 11.8%; 25 -48 - 23.6%; 49 -72
days - 37%. According to the literature, after 72
days of alcoholization, rats develop alcoholic poly-
neuropathy, the development of which was con-
firmed by an analgesimeter [16, 17].

Randall-Selitto tenso-algometric method. To confirm
the development of neuropathy, the Randall-Selitto
tensoalometric method was used [18, 19]. The an-
algosimeter was used to record the pain sensitivity
threshold (PST), which was determined by pressing
on the hind leg. A metal cylindrical nozzle with an
area of 0.5 cm² was used to determine the hind leg
pain threshold in rats of three months of age. The
pain threshold was the pressure recorded at the
time of the animal’s pronounced pain reaction
(squeaking or pulling out the paw). The pressure
was perceived by a strain gauge, converted into an
electrical signal, then processed and displayed
graphically and digitally on a computer monitor.
The average value of the threshold of pain sensitivity,
determined before the start of neuropathy modeling,
was taken as 100%.

PST in rats modeling diabetic neuropathy was de-
termined before modeling diabetes mellitus, on days
14 and 30 after streptozocin injection. PST in rats
modeling toxic neuropathy was determined before
paclitaxel administration, on days 16 and 25 after
the first injection of paclitaxel. The PST in rats mod-
eled with alcohol neuropathy was measured before
alcoholization and after 24, 48, 72 days of alcohol
consumption.

Animals were withdrawn from the experiment by
bleeding under thiopental anesthesia. Sodium thiop-
tal (ARTERIUM, Ukraine) was administered in-
trapерitoneally at a dose of 50 mg/kg. For biochemi-
cal studies, the homogenate of the studied rat ti-
sues was used, which was prepared by homogeni-
zation in 10 mM Tris-HCl buffer, pH 7.4; centrifuga-
tion for 10 minutes at 1000 rpm. The supernatant
was used for biochemical studies.

In the homogenate of periodontal soft tissues, total
proteolytic and total antiripic activities were deter-
mained by Veremeenko K.N., catalase activity by
Korolyuk M.A. et al., the content of Thiobarbituric
acid reactive substances (TBARS) by Stalna I.D.,
average mass molecules by Gabriyan N.I., oxida-
tively modified proteins by Dubinina E.E, fucose and
glycosaminoglycans (GAG) by Sharaev P.N. In the
homogenate of rat salivary glands, total proteolytic
and total antiripic activities, catalase activity, con-
tent of TBARS, average mass molecules, oxidatively
modified proteins and amylase activity were deter-
mained by Caraway W.T.

The level of total, protein-bound, and non-protein
sulfhydryl groups in the blood serum was deter-
mained by the Elman method [20]. Glutathione
peroxidase activity (EC 1.11.1.9) was determined by
combining the use of hydrogen peroxide and re-
duced glutathione as substrates and detecting a de-
crease in the amount of glutathione in the reaction
with 5,5’-dithiobis(2-nitrobenzoic) acid [21]. The ac-
tivity of glutathione transferase (EC 2.5.1.18) was
determined by the rate of formation of GSH conjuga-
gate with 1-chloro-2,4-dinitrobenzene [21]. Glu-
tathione reductase activity (EC 1.8.1.7) was meas-
ured by the decrease in the optical density of sam-
ple as a result of NADPH oxidation. [21]. To deter-
mine the content of reduced and oxidized glu-
tathione, the spectrofluorimetric method using or-
thopHALIC aldehyde at different pH values of the
medium was used [22]. The activity of superoxide
dismutase was determined by the method with ni-
troblue tetrazolium according to [21]. The content of
diene conjugates was determined in the heptane-
isopropanol extract by spectrophotometric method,
and the content of Schiff bases was determined by
the fluorometric method [21].

The obtained results of the experimental studies
were analyzed using the methods of variation statis-
tics. To check the distribution for normality, the
Shapiro-Wilk test was used to calculate the Shapiro-
Wilk test. If the data corresponded to a normal dis-
tribution, then the reliability of their difference when
comparing arithmetic means was determined using
Student’s t-test for independent samples; reliable
data were considered to be those that correspond to
p<0.05. In cases where the data series did not fol-
low a normal distribution, statistical processing was
performed using a nonparametric method - the
Mann-Whitney test.

Statistical processing of the study results was per-
formed on a PC using Microsoft Excel for Windows
Professional and included the determination of the
mean values of the parameters (M), and the mean
error (±m).

Results

We have found that streptozocin in rats caused dia-
betes mellitus with the development of diabetic neu-
ropathy, which was manifested by an increase in the
pain sensitivity threshold (PST), which was meas-
ured by the tensoalgometric method. As a result of
the studies, it was found that in control animals the
initial PST was 100.1±3.4% and on days 14 and 28
of measurement it fluctuated slightly within the base-
line. In rats modeled with streptozocin-induced neu-
ropathy, PST increased significantly on all days of
measurement compared to the initial value: on day 14 after streptozocin administration, PST increased by 22.4±8.4% (p<0.05), and on day 28 - by 100.9±15.3% (p<0.001). In animals on day 16 after paclitaxel administration, the PST increased by 39.0% (p<0.01) compared to day zero. The results confirm the literature data that paclitaxel causes toxic polyneuropathy, in which the speed of impulses along the nerve fiber decreases. Various studies have reported direct damage to peripheral nerves, loss of neuronal fibers and demyelination caused by paclitaxel, microtubule disruption and, as a result, impaired axonal transport of major cellular components cause degeneration of distal nerve segments and axonal membrane remodeling [23]. Studies by Duggett N.A. et al. indicate that most of the neurotoxic damage caused by paclitaxel is directed to the dorsal root ganglia and peripheral sensory nerves, which include the trigeminal [24].

Before alcoholization of the animals in the control and experimental groups, PST was equal to 100±10.8% in both groups. During the modeling of alcoholic neuropathy, PST in rats of the control group did not undergo statistically significant changes. In the rats of the experimental group, which were administered ethanol of increasing concentration for 72 days, the PST did not change on day 24 of the experiment, and on day 48 it increased by 45.4% (p<0.05), on day 72 - by 62.9% (p<0.05) relative to the initial value and animals of the control group, which, according to the literature, indicates the development of alcoholic neuropathy. Thus, the increase in PST measured by the tensosialographic method in the modeling of diabetic, toxic and alcohol-induced neuropathy confirms their development.

The development of diabetic polyneuropathy in rats was accompanied by the accumulation of lipid peroxidation products in the blood serum. Thus, in rats with diabetic polyneuropathy, the content of diene conjugates in the blood serum increased 1.5-fold compared with the control (Table 1).

<table>
<thead>
<tr>
<th>Groups of rats</th>
<th>Diene conjugates, nmol × mg protein⁻¹</th>
<th>TBARS, nmol × mg protein⁻¹</th>
<th>Schiff bases, units × mg protein⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Intact</td>
<td>36.55 ± 3.19</td>
<td>16.25 ± 1.68</td>
<td>± 0.41</td>
</tr>
<tr>
<td>n=9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Diabetic neuropathy</td>
<td>56.35 ± 4.22²</td>
<td>29.43 ± 2.36²</td>
<td>8.42 ± 0.59²</td>
</tr>
<tr>
<td>n=10</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* – P₁₋₂ < 0.05

In rats with diabetic polyneuropathy, the content of TBARS in the blood serum increased 1.7 times compared to the control. The content of Schiff bases in the blood serum of rats with diabetic polyneuropathy increased 1.6 times compared to the control (Table 1).

In rats with diabetic polyneuropathy, the content of TBARS products in the blood serum increased 1.7 times compared to the control. The content of Schiff bases in the blood serum of rats with diabetic polyneuropathy increased 1.6 times compared to the control (Table 1).

It has been shown that in diabetic neuropathy, the content of oxidatively modified proteins (OMP) in the blood serum of rats increases: neutral aldo-derivatives - 1.5 times, neutral keto-derivatives - 1.3 times, alkaline aldo-derivatives - 1.7 times and alkaline keto-derivatives - 2 times compared to these indicators in control animals (Table 2).

<table>
<thead>
<tr>
<th>Groups of rats</th>
<th>Parameters</th>
<th>Neutral products</th>
<th>Alkaline products</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Neutral products</td>
<td>Alkaline products</td>
<td></td>
</tr>
<tr>
<td>356 nm, aldo-derivatives</td>
<td>0.106 ± 0.008</td>
<td>0.167 ± 0.012²</td>
<td></td>
</tr>
<tr>
<td>370 nm, keto-derivatives</td>
<td>0.109 ± 0.009</td>
<td>0.157 ± 0.011¹</td>
<td></td>
</tr>
<tr>
<td>430 nm, aldo-derivatives</td>
<td>0.095 ± 0.008</td>
<td>0.168 ± 0.012²</td>
<td></td>
</tr>
<tr>
<td>530 nm, keto-derivatives</td>
<td>± 0.004</td>
<td>0.089 ± 0.007²</td>
<td></td>
</tr>
</tbody>
</table>

* – P₁₋₂ < 0.05

In rats with diabetic polyneuropathy, the serum content of sulfhydryl groups decreased: non-protein, protein SH-groups - by 1.4 times and total SH-groups - by 1.5 times compared to the control (Table 3).
Table 3: Content of sulfhydryl groups in the blood serum of animals with diabetic neuropathy, μmol × mg of protein⁻¹

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Groups of rats</th>
<th>non-protein SH- groups</th>
<th>protein SH- groups</th>
<th>total SH-groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. Intact</td>
<td>0.222 ± 0.019</td>
<td>4.369 ± 0.391</td>
<td>4.790 ± 0.343</td>
</tr>
<tr>
<td></td>
<td>n=9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Diabetic neuropathy</td>
<td>0.169 ± 0.012</td>
<td>3.387 ± 0.319*</td>
<td>3.125 ± 0.244*</td>
</tr>
<tr>
<td></td>
<td>n=10</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*– P₁₋₂ < 0.05

Under conditions of diabetes-induced neuropathy, superoxide dismutase activity in the blood serum increased 1.5 times and catalase activity decreased 1.4 times. Since superoxide dismutase inactivates the superoxide anion radical through its dismutation into hydrogen peroxide, which is catalyzed by catalase, the increased superoxide dismutase activity against the background of decreased catalase activity indicates the accumulation of hydrogen peroxide in the blood serum under conditions of streptozocin-induced neuropathy.

Table 4: Activity of antioxidant enzymes in the blood serum of rats with diabetic neuropathy

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Groups of rats</th>
<th>SOD activity, units × min⁻¹ × mg protein⁻¹</th>
<th>Catalase activity, nmol × min⁻¹ × mg protein⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. Intact</td>
<td>0.058 ± 0.004</td>
<td>2.29 ± 0.21</td>
</tr>
<tr>
<td></td>
<td>n=9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Diabetic neuropathy</td>
<td>0.103 ± 0.008*</td>
<td>1.54 ± 0.15*</td>
</tr>
<tr>
<td></td>
<td>n=10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*– P₁₋₂ < 0.05

Our further experiments were aimed at studying the glutathione-dependent link of the antioxidant system, which includes glutathione and glutathione-dependent enzymes - glutathione peroxidase, glutathione transferase and glutathione reductase - in the blood serum of rats with diabetic polyneuropathy.

Table 5: The content of reduced and oxidized glutathione, activity of glutathione system enzymes in the blood serum of rats with diabetic polyneuropathy

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Groups of rats</th>
<th>Reduced glutathione, nmol GSH/ mg protein</th>
<th>Oxidized glutathione, nmol GSSG/ mg protein</th>
<th>Glutathione reductase, nmol NADPH/ min × mg protein</th>
<th>Glutathione transferase, nmol /min×ml</th>
<th>Glutathione peroxidase, μmol GSH/ min×ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. Intact</td>
<td>1.00±0.01</td>
<td>0.319±0.003</td>
<td>36.25±2.14</td>
<td>323.65±12.98</td>
<td>54.23±2.19</td>
</tr>
<tr>
<td></td>
<td>n=9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Diabetic neuropathy</td>
<td>1.04±0.03</td>
<td>0.269±0.005*</td>
<td>21.36±0.72*</td>
<td>289.05±21.23*</td>
<td>36.12±1.97*</td>
</tr>
<tr>
<td></td>
<td>n=10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*– P₁₋₂ < 0.05

Diabetic polyneuropathy did not affect the level of reduced glutathione in the blood serum of rats. In the serum of rats with diabetic polyneuropathy, the level of oxidized glutathione decreased by 1.2 times compared to the control. The activity of glutathione reductase in the blood serum of rats with diabetic polyneuropathy was 1.8 times lower than in the control. The activity of glutathione transferase in rats with diabetic polyneuropathy was reduced by 1.2 times compared to the control. In rats with diabetic polyneuropathy, the activity of glutathione peroxidase decreased by 1.5 times compared to the control (Table 5).

Table 6: The content of lipid peroxidation products in the blood serum of rats with toxic neuropathy

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Groups of rats</th>
<th>Diene conjugates, nmol × mg protein⁻¹</th>
<th>TBARS, nmol × mg protein⁻¹</th>
<th>Schiff bases, units × mg protein⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. Intact</td>
<td>36.45 ± 3.29</td>
<td>16.22 ± 1.64</td>
<td>3.89 ± 0.38</td>
</tr>
<tr>
<td></td>
<td>n=9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Toxic neuropathy</td>
<td>71.02 ± 5.96*</td>
<td>36.24 ± 1.98*</td>
<td>11.02 ± 0.94*</td>
</tr>
<tr>
<td></td>
<td>n=9</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*– P₁₋₂ < 0.05

In rats with toxic neuropathy, the serum content of diene conjugates, TBARS, and Schiff bases increased by 1.8, 1.9, and 2.3 times, respectively, compared with these values in intact animals (Table 6).
It has been shown that in toxic neuropathy, the content of OMP products also increased in the blood serum of rats: the content of neutral products with absorption peaks at 356 nm and 370 nm increased by 1.5 and 1.7 times, respectively, compared to the control (Table 7).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Neutral products</th>
<th>Alkaline products</th>
</tr>
</thead>
<tbody>
<tr>
<td>356 nm, aldo-derivatives</td>
<td>0.106 ± 0.008</td>
<td>0.109 ± 0.009</td>
</tr>
<tr>
<td>370 nm, keto-derivatives</td>
<td>0.095 ± 0.008</td>
<td>0.039 ± 0.004</td>
</tr>
</tbody>
</table>

* - Ș2 < 0.05

Another important indicator of protein modification is the oxidation of their sulfhydryl groups, which can occur both directly and enzymatically with the participation of glutathione peroxidase and lipid hydroperoxides. It has been shown that in paclitaxel-treated rats, the content of sulfhydryl groups in the blood serum also decreased: non-protein SH-groups - by 1.5 times, protein SH-groups - by 1.3 times, and total SH-groups - by 1.4 times compared to the control (Table 8).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Non-protein SH-groups</th>
<th>Protein SH-groups</th>
<th>Total SH-groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Intact</td>
<td>0.221 ± 0.019</td>
<td>4.463 ± 0.399</td>
<td>4.689 ± 0.358</td>
</tr>
<tr>
<td>2. Toxic neuropathy</td>
<td>0.159 ± 0.013*</td>
<td>3.298 ± 0.319*</td>
<td>3.395 ± 0.342*</td>
</tr>
</tbody>
</table>

* - Ș2 < 0.05

The damaging effect of free radical processes is counteracted by the antioxidant system of cells, which is able to limit it through the coordinated work of enzymatic and non-enzymatic control mechanisms. We evaluated the state of the antioxidant system by the activity of antiradical enzymes: superoxide dismutase and catalase.

Under conditions of paclitaxel-induced neuropathy, the activity of superoxide dismutase decreased in the serum of rats by 3.9 times, and catalase activity - by 1.6 times compared with these values in control rats (Table 9).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>SOD activity, units × min⁻¹ × mg protein⁻¹</th>
<th>Catalase activity, nmol × min⁻¹ × mg protein⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Intact</td>
<td>0.058 ± 0.004</td>
<td>2.29 ± 0.21</td>
</tr>
<tr>
<td>2. Toxic neuropathy</td>
<td>0.016 ± 0.001*</td>
<td>1.41 ± 0.12*</td>
</tr>
</tbody>
</table>

* - Ș2 < 0.05

The activity of glutathione reductase in the blood serum of rats with toxic neuropathy was 1.4 times lower than in the control (Table 10). Other indicators of the glutathione system in the blood serum did not change statistically under conditions of toxic neuropathy.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Reduced glutathione, nmol GSH/ mg protein</th>
<th>Oxidized glutathione, nmol GSSG/ mg protein</th>
<th>Glutathione reductase, nmol NADPH/ min × mg protein</th>
<th>Glutathione transferase, nmol /min*ml</th>
<th>Glutathione peroxidase, μmol GSH/ min*ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Intact</td>
<td>1.00±0.010</td>
<td>0.319±0.003</td>
<td>36.250±2.14</td>
<td>323.65±12.98</td>
<td>54.23±2.19</td>
</tr>
<tr>
<td>2. Toxic neuropathy</td>
<td>1.011±0.012*</td>
<td>0.328±0.007</td>
<td>27.099±1.12*</td>
<td>311.47±12.29</td>
<td>61.37±4.23</td>
</tr>
</tbody>
</table>

* - Ș2 < 0.05

It is known that the largest amount of enzymes produced by the large salivary glands is amylase, which belongs to carbohydrate digestive enzymes that hydrolyze the alpha-1,4-glycosidic bonds of amylose. We found that under conditions of experimental diabetic neuropathy, the activity of α-amylase in the
submandibular and sublingual salivary glands of rats was significantly reduced by half compared with intact animals (Table 11). Under conditions of modeling paclitaxel-induced neuropathy, amylolytic activity in the salivary glands of animals significantly decreased by 1.6 times compared to the group of intact rats (Table 11). Prolonged administration of increasing concentrations of ethyl alcohol led to a significant decrease in the activity of salivary α-amylase by 1.7 times compared with intact animals (Table 11). Thus, under the conditions of streptozocin-induced, toxic and alcoholic neuropathies, the protein synthetic function of the salivary glands is suppressed. In our opinion, the decrease in the amylolytic activity of the salivary glands of animals under the conditions of modeling neuropathies of various genesis is associated with the inhibition of protein synthesis function and due to conformational changes in the enzyme that occur under the influence of highly reactive lipid peroxidation products.

Table 11. Changes in biochemical parameters in salivary glands of rats under conditions of toxic, diabetic and alcoholic polyneuropathy

<table>
<thead>
<tr>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Total proteolytic activity, μg/g•min</td>
<td>3.33±0.06 (n = 9)</td>
<td>2.79±0.19 (n = 25)</td>
<td>3.24±0.1 (n = 11)</td>
<td>3.11±0.42 (n = 5)</td>
</tr>
<tr>
<td>2</td>
<td>Total antitrypsin activity, g/kg</td>
<td>32.64±1.74 (n = 9)</td>
<td>55.94±6.53* (n = 20)</td>
<td>89.77±7.01*** (n = 11)</td>
<td>36.25±5.38** (n = 5)</td>
</tr>
<tr>
<td>3</td>
<td>Activity of α-amylase, mg/s*</td>
<td>38.8±6.7 (n = 10)</td>
<td>23.75±1.61* (n = 25)</td>
<td>20.18±2.66* (n = 11)</td>
<td>22.83±1.78*** (n = 5)</td>
</tr>
<tr>
<td>4</td>
<td>Content of TBARS, μmol/g</td>
<td>4.25±0.72 (n = 15)</td>
<td>9.62±1.14* (n = 18)</td>
<td>8.72±1.16* (n = 11)</td>
<td>5.87±0.47** (n = 5)</td>
</tr>
<tr>
<td>5</td>
<td>Content of average mass molecules, n.u.</td>
<td>0.294±0.003 (n = 8)</td>
<td>0.414±0.019* (n = 25)</td>
<td>0.32±0.009** (n = 11)</td>
<td>0.39±0.021*** (n = 5)</td>
</tr>
<tr>
<td>6</td>
<td>Content of oxidatively modified proteins, n.u.</td>
<td>0.36±0.02 (n = 10)</td>
<td>0.46±0.03* (n = 26)</td>
<td>0.37±0.03* (n = 11)</td>
<td>1.20±0.14**** (n = 5)</td>
</tr>
<tr>
<td>7</td>
<td>Catalase activity, μkat/g•min</td>
<td>0.74±0.034 (n = 10)</td>
<td>0.35±0.047*** (n = 18)</td>
<td>0.84±0.06*** (n = 11)</td>
<td>0.68±0.06** (n = 6)</td>
</tr>
</tbody>
</table>

* P<0.05  ** P<0.01  *** P<0.001  ^^ P<0.0001  ^ P<0.005  # P>0.05  ## P>0.01  ### P>0.05

Under the conditions of modeling toxic, diabetic and alcoholic polyneuropathy, the activity of α-amylase in the salivary glands of rats significantly decreased compared to control animals (Table 11), indicating the inhibition of protein synthetic activity of large salivary glands under these conditions.

It is known that free radical oxidation products of lipids are biomarkers of cell damage, since their content can be used to assess the intensity of free radical processes and the degree of oxidative stress.

Primary products of lipid peroxidation (lipid hydroperoxides, diene conjugates) are unstable compounds that are metabolized rather rapidly to form secondary, more stable liperoxidation products, the content of which is determined to assess the prooxidant system. Among them, one of the most sensitive markers of lipid peroxidation and oxidative stress is malondialdehyde, a secondary product of the oxidation of polyene higher fatty acids of the cytoplasmic membrane of cells, which is formed as a result of their oxidative degradation by reactive oxygen species. However, not only malondialdehyde, but also other substances formed during liperoxidation processes react with thiobarbituric acid, so we determined the content of TBARS.

Fatty acid peroxides are unstable; as a result of carbon-carbon bond breaking, they form highly reactive, toxic aldehydes, which not only have membrane-destructive effects, unlike free radicals, but are more stable and easily diffuse over long distances and contribute to covalent modification of biomolecules. At present, the cytotoxic effect of excess carbonyl compounds has been experimentally confirmed [25].

Proteins are also sensitive targets for the effects of reactive oxygen and nitrogen species, which leads to changes in their spatial organization, aggregation, and fragmentation. An integral indicator of carbonyl stress is the content of oxidatively modified proteins (OMP). The degree of protein damage depends on the amino acid composition, native nature, i.e., the accessibility of amino acid residues to reactive oxygen species, the effect of which can be different, for example, hydroxyl radical causes protein aggregation, and superoxide anion radical causes mostly protein fragmentation. It is believed that OMP is one of the earliest and most reliable biomarkers of cell damage in free radical pathology.

We found that under the conditions of streptozocin-induced neuropathy, carbonyl oxide stress does not develop in the major salivary glands of rats, which confirms the absence of significant changes in the content of oxidatively modified proteins compared with intact animals (Table 11). Analyzing the content of average mass molecules under conditions of diabetic neuropathy, we found a significant increase by 9% compared to the group of intact animals (Table 11).
A significant difference in the content of average mass molecules in the large salivary glands was found between the groups of rats with paclitaxel-induced and streptozocin-induced neuropathy. The highest catalase activity in salivary glands of animals was observed in diabetic neuropathy, which was 2.5 times higher compared to rats with toxic neuropathy and 1.3 times higher compared to rats with alcoholic neuropathy. Under conditions of prolonged alcoholization of animals, catalase activity was significantly 1.9 times higher compared to the group of animals with toxic neuropathy (Table 11).

Thus, under the conditions of experimental diabetic neuropathy reproduction, lipid peroxidation processes are activated in the tissues of the submandibular and sublingual salivary glands of rats against the background of increased antiradical defense, indicating a decompensatory balance of the pro- and antioxidant system. The reproduction of paclitaxel-induced neuropathy is accompanied by the development of carbonyl-oxidative stress in the salivary glands of rats. Under conditions of prolonged alcoholization of animals, an imbalance of the pro- and antioxidant system is observed in the salivary glands.

The proteinase-inhibitor balance of large salivary glands of animals was analyzed based on the determination of total proteolytic activity and antitryptic activity. It is known that salivary glands produce a large number of proteolytic enzyme inhibitors. Analyzing the total antitryptic activity in the salivary glands of rats, it was found to increase by 2.75 times in streptozocin-induced diabetic neuropathy and by 1.71 times in paclitaxel-induced neuropathy compared with these values in intact animals (Table 11). No significant changes in the total antitryptic activity in the salivary gland tissues of rats with the development of alcoholic neuropathy were detected (Table 11).

The total antitryptic activity in the salivary glands of rats with diabetic neuropathy was significantly higher by 1.6 and 2.5 times compared to animals modeled with toxic and alcoholic neuropathy, respectively. No statistically significant changes in the total proteolytic activity in the salivary glands of animals of all study groups under conditions of neuropathy of different genesis were found (Table 11).

Thus, under the conditions of reproduction of experimental diabetic and toxic neuropathies in the salivary glands of animals, changes in the proteinase-inhibitor balance of the compensatory type are observed. Alcoholization of animals does not cause changes in the proteinase-inhibitor balance of the salivary glands.
Table 12.
Changes in biochemical parameters in soft tissues of periodontium of rats under conditions of toxic, diabetic and alcoholic polyneuropathy

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Total proteolytic activity, µg/g.min.</td>
<td>3.17±0.01</td>
<td>2.8±0.19^</td>
<td>3.41±0.03^^</td>
<td>2.75±0.08***</td>
</tr>
<tr>
<td>2</td>
<td>Total antitrypsin activity, g/kg</td>
<td>33.19±1.31</td>
<td>41.25±1.07''**</td>
<td>53.85±0.71''***</td>
<td>30.00±0.63***</td>
</tr>
<tr>
<td>3</td>
<td>Content of TBARS, µmol/g</td>
<td>2.41±0.11</td>
<td>3.17±0.18''</td>
<td>4.45±0.03''***</td>
<td>4.21±0.13''***</td>
</tr>
<tr>
<td>4</td>
<td>Content of polyglycans, µmol/g</td>
<td>0.29±0.02</td>
<td>0.33±0.01*</td>
<td>0.31±0.01**</td>
<td>0.32±0.01***</td>
</tr>
<tr>
<td>5</td>
<td>Content of oxidatively modified proteins, n.u.</td>
<td>1.35±0.025</td>
<td>1.89±0.032''</td>
<td>1.76±0.03**</td>
<td>1.74±0.03***</td>
</tr>
<tr>
<td>6</td>
<td>Catalase activity, µkat/g.min.</td>
<td>0.27±0.04</td>
<td>0.38±0.025''</td>
<td>0.11±0.01''***</td>
<td>0.36±0.03***</td>
</tr>
<tr>
<td>7</td>
<td>GAG content, µmol/g</td>
<td>0.61±0.05</td>
<td>2.32±0.067''</td>
<td>0.99±0.03''***</td>
<td>1.68±0.17''***</td>
</tr>
<tr>
<td>8</td>
<td>Fucose content, µmol/g</td>
<td>7.93±0.19</td>
<td>10.61±0.38*</td>
<td>10.25±0.31**</td>
<td>10.90±0.15**</td>
</tr>
</tbody>
</table>

Under the conditions of toxic polyneuropathy development, the content of glycosaminoglycans in the periodontal tissues of rats increased by 3.8 times and the content of free fucose by 1.3 times compared to intact animals (Table 12). Under the conditions of diabetic polyneuropathy development, the content of free fucose in the periodontal tissues of rats increased by 1.3 times and the content of glycosaminoglycans by 1.6 times compared to intact animals (Table 12). Analyzing the content of free fucose as a monomer of fucoproteins and GAG as heteropolysaccharides of proteoglycans in rat periodontal tissues under conditions of 72-day administration of ethyl alcohol of increasing concentration, we obtained, respectively, an increase of 1.4 times and 2.8 times compared to intact animals (Table 12). Under the conditions of toxic, diabetic and alcoholic polyneuropathies, the content of GAG and free fucose in rat periodontal tissues increased compared to these indicators in control animals, which indicates that polyneuropathies of various genesis cause increased catabolism of biopolymers of the extracellular matrix of the connective tissue of the rat periodontium.

Remodeling processes of the extracellular matrix of the periodontal connective tissue are an important prerequisite for maintaining the integrity of the dentition and fixation of the tooth in the alveolus. Remodeling is controlled by metalloproteinases, the balance of which depends on the overall inhibitory activity, so it is important to study the proteinase-inhibitory potential of periodontal tissues in the modeling of polyneuropathies of various genesis.

We found a significant decrease in the total proteolytic activity in the soft tissues of periodontium of rats with paclitaxel-induced polyneuropathy by 12% compared to intact animals. The total antitrypsin activity significantly increased in the periodontal tissues of animals with toxic polyneuropathy by 20% compared to intact animals, indicating changes in the proteinase-inhibitor balance of the compensatory type (Table 12). Analyzing the proteinase-inhibitor balance in the soft tissues of the periodontium of rats with diabetic polyneuropathy, a significant increase in total proteolytic activity by 1.6 times was found against a significant increase in total antitrypsin activity by 1.1 times compared to intact animals (Table 12). We found that 72-day administration of ethyl alcohol of increasing concentration in rats reduced the total proteolytic activity in periodontal tissues by 13.5% against the background of a decrease in the activity of proteinase inhibitors by 7.8% (Table 12).

Paclitaxel-induced polyneuropathy is accompanied by the development of carbonyl-oxidative stress in the soft tissues of the rat periodontium, as evidenced by a significant increase in the content of oxidatively modified proteins by 29% and the content of TBARS by 25% compared to these indicators in intact animals. Catalase activity in periodontal tissues of animals significantly increased by 1.4 times after paclitaxel administration. Under these conditions, there was also an increase in the content of average mass molecules by 12% (Table 12). Under the conditions of diabetic polyneuropathy, on day 30 of the experiment, we found the development of oxidative stress in the periodontal tissues of animals, as evidenced by a significant increase in the content of TBARS by 46%, oxidatively modified proteins by 23% and medium weight molecules by 12%. Catalase activity in periodontal tissues of animals signifi-
cantly decreased by 59% in diabetic polyneuropathy compared to intact animals (Table 12). Under the conditions of development of alcoholic polyneuropathy, on day 72 of the experiment, we found the development of oxidative stress in the soft tissues of the periodontium of animals, as evidenced by a significant increase in the content of oxidatively modified proteins by 1.3 times in the periodontal tissues of rats against the background of an increase in catalase activity by 1.3 times compared with these indicators in intact animals. Under these conditions, an increase in the content of secondary products of lipid peroxidation of TBARS by 1.7 times, as well as an increase in the content of average mass molecules by 1.1 times compared to these indicators in intact animals was observed (Table 12).

All three types of polyneuropathies are accompanied by the development of carbonyl-oxidative stress in the soft tissues of the rat periodontium, as evidenced by a significant increase in the content of oxidatively modified proteins and the content of TBARS compared to these indicators in intact animals. Under these conditions, there is also an increase in the content of average mass molecules compared to the control.

**Discussion**

The pathogenesis of diabetic neuropathy is multifactorial, including increased mitochondrial free radical production due to hyperglycemia-induced oxidative stress. Mechanisms that affect neuronal activity, mitochondrial function, membrane permeability, and endothelial function include the formation of advanced glycosylation end products, activation of polyol-aldose reductase signaling, activation of poly(ADP-ribose) polymerase, and alteration of Na+/K+-ATPase function. Thus, in the pathophysiology of diabetic neuropathy, three main mechanisms are distinguished: oxidative stress, glucotoxicity with the formation of progressive glycosylation end products, and endothelial dysfunction that occurs in the setting of microangiopathy [26,27].

Streptozocin-induced diabetic neuropathy promotes the development of pathological changes in the submandibular and sublingual salivary glands of rats, as evidenced by impaired protein synthetic function, changes in proteinase-inhibitory and pro/antioxidant balance. Oxidative stress develops in the periodontal soft tissues, which, together with proteinase-inhibitor imbalance, contributes to increased depolymerization of glycoconjugates of periodontal connective tissue.

It is known that paclitaxel is able to interact with β-tubulin of microtubules of the cell cytoskeleton, inhibiting dynamic polymerization and depolymerization, which leads to their stabilization, cell cycle arrest and death. Stabilization of microtubules is the main mechanism of action of taxanes and is responsible for their antitumor activity [28], but this mechanism is not the only one in the development of neurotoxicity and there is already sufficient evidence of impaired neuronal and glial cell metabolism, mitochondrial dysfunction, oxidative stress and neuroinflammation underlying the development of paclitaxel-induced neuropathy [29]. Paclitaxel causes an increase in the production of pro-inflammatory cytokines (TNF alpha and IL-1 beta) and a decrease in anti-inflammatory cytokines (IL-4 and IL-10) [30], which leads to the recruitment and activation of immune cells and the development of neuroinflammation [31]. Paclitaxel-induced neuropathy causes periodontal syndrome in rats, as evidenced by the development of carbonyl-oxidative stress, changes in the proteinase-inhibitor balance, which leads to increased breakdown of fucoproteins and proteoglycans of the extracellular matrix of periodontal connective tissue with subsequent tooth elimination.

Ethanol causes direct metabolic and toxic damage to neurons and glial cells. The main consequences include impaired astrocyte and oligodendrocyte function, leading to neuronal pathology, including reduced synaptogenesis, synapse maintenance, and cell survival. White matter pathology ranges from dysmyelination to demyelination and myelin degeneration, and it occurs in all forms of alcoholic CNS pathology [32]. Approximately 30 minutes after alcohol consumption, the concentration of ethanol in saliva and salivary glands is higher than in blood. Ivoš et al. (2019) reviewed the effects of ethanol on oral health, among which were damage to mucosal and glandular tissues, reduction in immune functions, an increased rate of various inflammatory oral diseases, peripheral neuropathy associated with sialadenosis, reduction of saliva excretion, precancerous lesions, or cancer [33]. It is well known that the development of oxidative stress due to ethanol intoxication occurs in several main ways: acetaldehyde mediates an increase in the amount of reactive nitrogen and oxygen species by inducing nitric oxide synthase, NADPH oxidase and xanthine oxidase at the post-transcriptional level [34]; reactive oxygen species due to mitochondrial labilization increase the Ca2+ concentration, which activates Ca2+-calmodulin-dependent protein kinase II [35]; increased production of reactive oxygen species by CYP2E1, which is capable of producing ethoxy radical, hydroxethyl radical, acetyl radical, singlet radical, superoxide radical, hydrogen peroxide, hydroxyl radical, alkoxyl radical and peroxy radical [36]. The redox imbalance is maintained by the depletion of NADPH, which is necessary for the regeneration of glutathione, an important antioxidant molecule and co-substrate for the antioxidant enzymes of the glutathione system. Periodontal syndrome in animals...
with ethanol-induced peripheral polyneuropathy occurs due to increased catabolism of connective tissue biopolymers against the background of oxidative stress and proteinase-inhibitor imbalance.

Under conditions of diabetic, toxic and alcoholic neuropathy, the amylolytic activity of large salivary glands of animals is suppressed compared to intact animals, which indicates a decrease in protein synthetic function and/or enzyme conformation due to activation of oxidative stress, which causes oxidative modification of proteins. The balance of the pro- and antioxidant system of salivary glands in animals with paclitaxel-induced neuropathy is decompensatory, as evidenced by the increase in prooxidants against the background of a probable decrease in catalase activity. Under conditions of diabetic neuropathy, the balance of the pro- and antioxidant system of the large salivary glands of animals is compensatory, as evidenced by the absence of statistically significant changes in the content of OMP against the background of a significant increase in catalase. In the conditions of modeling alcoholic neuropathy in animals, an imbalance of the pro- and antioxidant system occurs in the large salivary glands: an increase in prooxidants against the background of unchanged antiradical defense. The maximum development of carbonyl-oxidative stress in the salivary glands of animals was observed under conditions of alcoholic neuropathy compared to diabetic and toxic neuropathy. In the modeling of peripheral polyneuropathy in animals by administration of paclitaxel, streptozocin and ethanol, the development of periodontal syndrome development in paclitaxel-, streptozocin-, ethanol-induced peripheral polyneuropathy are increased catabolism of connective tissue glycoconjugates and the development of oxidative stress and proteinase-inhibitor imbalance.

**Conflict of interest:**
The authors declare no conflict of interest

**Ethical approval:**
Ethics approval and consent to participate the study was approved by the Committee on Bioethics and Ethical Issues of Poltava State Medical University (Minutes No. 181 of 26.03.2020).

**References**


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РОЗВИТОК ПАТОЛОГІЧНИХ ЗМІН У ОРГАНАХ ПОРОЖНЮ РОТА ТВАРИН ЗА УМОВ ПОЛІНЕЙРОПАТІЇ РІЗНОГО ГЕНЕЗУ

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2Навчально-науковий центр «Інститут біології та медицини» Київського національного університету імені Тараса Шевченка, м. Києв;

Метою дослідження було з’ясування впливу полінейропатії різного генезу на розвиток патологічних змін у великих слизових залозах та тканинах породи тварин.

Методи. Дослідження проведено на 62 лабораторних шурах обох статей. Токсичну полінейропатію індукували ін’єкцією палітакселю, експериментальну цукровий диабет 1-го типу моделювали введенням стрептоцину, алкогольну полінейропатію викликали шляхом тривалого введення етанолу зростаючої концентрації. Розвиток полінейропатії підтверджували за зміною порогу больової чутливості (ПБЧ) за допомогою тензоалгометричного методу Randall-Selitto. У гомогенатах органів ротової порожнини визначали загальну протеолітичну та загальну анти- тріпсінну активності, активність каталази, вміст ТБК-реактантів, молекул середньої маси, окисно-модифікованих протеїнів, фукози і глюкозаміногліканів (ГАГ) та активність амілази. В сироватці крові визначали рівень загальних,
Білок-зв'язаних та небілкових сульфгідрильних груп, активність супероксиддисмутази, глутатіонпероксидази, глутатіонтрансферази, глутатіонредуктази; вміст відновленого та окисненого глутатіону, дієнових кон’югатів та шиффових основ.

Результати. Нами встановлено зростання ПБЧ у тварин, яким моделювали нейропатії різного ґенезу. Усі три види полінейропатій супроводжуються розвитком карбонільно-оксидативного стресу у м'яких тканинах пародонта та великих слинних залозах щурів, про що свідчить вірогідне збільшення вмісту оксно-модифікованих білків та вмісту ТБК-реактантів, а також молекул середньої маси порівняно з цими показниками у інтактних тварин. За умов моделювання усіх трьох полінейропатій білок-синтетична активність великих слинних залоз пригнічується, про що свідчить зниження активності α-амілази. За умов відтворення експериментальної діабетичної та токсичної нейропатій у слинних залозах тварин спостерігаються зміни протеїназно-інгібіторного балансу за компенсаторним типом. Нами встановлено, що полінейропатії різного ґенезу спричинюють підвищення катаалазібополімерів естрадиол-тренного матрикса сполучної тканини пародонта щурів, що підтверджує збільшення вмісту ГАГ та вільної фукози порівняно з цими показниками у контрольних тварин.

Висновки. За умов діабетичної, токсичної та алкогольної нейропатії пригнічується амілолітична активність великих слинних залоз тварин, змінюється баланс про- та антиоксидантної системи. При моделюванні периферійної полінейропатії у тварин шляхом введення паклітакселу, стрептозоцину та етанолу спостерігається розвиток пародонтального синдрому, провідними патогенетичними механізмами розвитку якого є підвищення катаалазібополімерів гліко-кон’югатів сполучної тканини та розвиток оксидативного стресу і протеїназно-інгібіторного дисбалансу.

Ключові слова: полінейропатії, нейротоксичність, цукровий діабет, паклітаксел, поріг больової чутливості, етанол, слинні залози, пародонт.