

ORIGINAL ARTICLE

Systemic disorders of the oxidant-antioxidant system of the brain and kidney in scopolamine-induced Alzheimer's disease and their correction with carbacetam

Yevhen P. Drezna, Taras I. Kmet, Igor Sv. Davydenko, Ksenia V. Slobodian, Oksana V. Kushnir, Khrystyna I. Pudiak

BUKOVINIAN STATE MEDICAL UNIVERSITY, CHERNIVTSI, UKRAINE

ABSTRACT

Aim: To assess the state of the oxidant-antioxidant system of the hippocampus and kidneys of rats with scopolamine-induced Alzheimer's disease and with the administration of carbacetam, as a GABA receptor modulator, and to clarify the possible systemic oxidative process.

Materials and Methods: The experiments were carried out on mature and old male rats. Alzheimer's disease was simulated by scopolamine hydrochloride (Sigma, USA). It was introduced into the peritoneum in a dose of 1 mg/kg of the body weight once a day during 27 days. On the 28th day, carbacetam was administered in a dose of 5 mg/kg once a day during 14 days. Intensity of lipid peroxide oxidation (LPO) was evaluated by the content of products reacting with 2-thiobarbituric acid reactive substances (TBARS). The content of protein oxidation modification (POM), also known as protein oxidation, in homogenates was determined by the amount of their oxidative modification products with the help of spectrophotometric method. The state of antioxidant protection was assessed by catalase and SOD activity.

Results: Simulated Alzheimer's disease was found to cause affliction of the protein amino groups in the hippocampal neurons and endotheliocytes, and in the mesangial matrix of non-collapsed renal glomeruli of rats of different ages with more pronounced changes in brain cells. At the same time, there is a clear existing relationship between affliction of the nerve cells and kidneys, which makes a foundation for further study of pathogenic processes and interrelations in neurodegenerative processes.

Conclusions: Thus, the group of rats of different ages with experimental Alzheimer's disease presented increase of the lipid and protein peroxidation products with more pronounced lesion in the hippocampal cells than those of the kidneys. Moreover, decrease of the lipid and protein peroxidation products in the examined organs of rats with scopolamine-induced Alzheimer's disease after administration of carbacetam indicates the involvement of the GABA-ergic system in the pathogenesis of damage to hippocampal neurons and kidney cells.

KEY WORDS: scopolamine-induced Alzheimer's disease, carbacetam, lipid and protein peroxide oxidation, antioxidants, hippocampus, kidneys

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INTRODUCTION

Globally, dementia has become one of the most important social, economic and public issues of health care, which is associated with increasing human lifespan. Epidemiological studies have estimated that about 50 million people worldwide suffer from dementia. Alzheimer's disease accounts for 60 to 80% of all cases. According to forecasts, this number will triple by 2050 [1, 2]. The main risk factor of Alzheimer's disease incidence is old age [3]. However, recently kidney diseases have been suggested as a modified risk factor promoting the development of Alzheimer's disease. The foundation for this is the fact that kidneys and brain are the organs with similar anatomical and vascular systems, hemodynamic specific features, which make them prone to vascular damage [4]. Therefore, Alzheimer's disease and kidney

damage may have common risk factors and potential basic mechanisms.

The physiological function of the kidney is to maintain the stability of the internal environment, including cerebrovascular circulation, while impaired renal function often leads to ischemia and hypoxia. The high blood flow rate in the kidneys significantly exceeds the needs of their own metabolism. At the same time, oxygen consumption by the human brain is approximately 1/5 from oxygen consumption by the whole body. The amount of blood reaching the human brain is approximately 15% of total cardiac output. Normal blood pressure allows the brain to receive sufficient cerebral blood supply. Blood pressure balance depends on complicated regulatory mechanisms of the neurohumoral systems involving all the body organs, and the kidney is a center of the blood pressure regulation system [5].

From pathophysiological view, Alzheimer's disease is known to contain a vascular component, and the cause of cognitive decline is multifaceted. Contrary to this, individuals with kidney failure present a disproportionately high degree of cerebrovascular diseases, which can be a significant cause of development and advance of cognitive decline [5].

According to the scientific evidence, gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter of the central nervous system. The acid plays a key role in the CNS physiology, simulating various processes, participates in many pathological processes: sleep disorders, depression, anxiety, alcohol abuse, and premenstrual syndrome [6, 7]. The same subtype of GABA receptors is known to possess a different nature of the cellular population and subcellular expression in different portions of the brain, stimulating excitability and neuronal synchronization in various pathologies and conditions [8]. The scientific literature presents evidence concerning their considerable presence in the kidneys [10]. For example, activation of endogenous GABA and glutamate receptors in the kidneys is known to significantly change the diameter of microvessels alternating renal blood flow [9]. GABA effect produced on the renal capillaries is very much alike the effect, which is the central one to regulate the central nervous system capillaries. Since regulatory disorders of the renal blood flow are associated with chronic kidney diseases and changes in the renal GABA system, possibly by means of prescription drugs, long-term kidney function can be significantly affected.

In recent decades, numerous hypotheses have made attempts to explain interrelationship between these two diseases (Alzheimer's disease and kidney dysfunction), which are multifactorial by their nature. However, irrespective of the facts, the underlying mechanisms of this correlation remain unclear. At the same time, the scientific literary sources available do not contain information about Alzheimer's disease effect of kidney condition.

AIM

Therefore, the aim of our study was to assess the state of the oxidant-antioxidant system of the hippocampus and kidneys of rats with scopolamine-induced Alzheimer's disease and with the administration of carbacetam, as a GABA receptor modulator, and to clarify the possible systemic oxidative process.

MATERIALS AND METHODS

The experiments were performed on male rats of mature (0.21-0.24 kg) and old (0.41-0.44 kg) age, which

were kept under standard vivarium conditions at a temperature of 18-22 °C and a relative humidity of 40-60%, on a balanced diet with free access to water under conditions of natural day and night cycles. Twenty-two mature and 23 old rats were used for this study. All the experimental procedures were carried out according to the main principles of the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes.

Given the general acceptance of the cholinergic hypothesis in the pathogenesis of Alzheimer's dementia, studies were conducted in rats with a scopolamine-induced model [10]. The model we used focuses on reproducing cognitive impairments and specific behavioral deficits. It allows us to assess the consequences of the disorders, but does not fully reproduce the pathogenesis of the neurodegenerative disease. It was modeled by the administration of scopolamine hydrochloride (Sigma, USA) intraperitoneally at a dose of 1 mg/kg body weight once a day for 27 days [11]. On the 28th day, carbacetam was administered in a dose of 5 mg/kg once a day during 14 days. Euthanasia of rats was performed under light chloroform narcosis. The brain and kidneys were removed in the cold and thoroughly washed with cooled 0.9 % NaCl solution. The hippocampus was isolated using a stereotaxic atlas [12]. Cytoplasmic fraction was isolated by means of differential centrifugation of homogenate of the examined structures in a refrigerated centrifuge at 1000 g for 10 min, followed by 1400 g for 10 min at the temperature of 4°C. LPO intensity was evaluated by the content of products reacting with 2-thiobarbituric acid reactive substances (TBARS) [13]. TBARS amount was calculated in μmol per 1 g of tissue. The content of protein oxidation modification (POM), also known as protein oxidation, in homogenates was determined by the amount of their oxidative modification products with the help of spectrophotometric method. At a wavelength of $\lambda=370$ nm, ketone dinitrophenyl hydrozones of neutral character were determined, at $\lambda=430$ nm – aldehyde dinitrophenyl hydrozones of basic character were determined [14]. POM content was expressed in units per g of tissue. The state of the antioxidant defense system was assessed by the activity of superoxide dismutase (SOD) and catalase [15].

Brain samples for histological examination were fixed in 10 % neutral formalin solution and after standard histological processing the tissue was embedded in paraffin. Paraffinic histological sections of the hippocampal and kidney tissues 5 μm (microns) thick were made with a sled microtome MS-2. Quantitative assessment of the protein state in histochemical samples stained with bromophenol blue according to Mikel Calvo was carried out by computer microspectrophotometry based on the R/B ratio [16].

Table 1. Effect of carbaracetam on indices of the prooxidant system of the hippocampus and kidneys of rats of different ages with scopolamine-induced Alzheimer's disease, $M \pm m$

Indices	Age	Control	Scopolamine-induced Alzheimer's disease	Scopolamine-induced Alzheimer's disease + carbacetam
hippocampus				
TBA AP mcmol/g of tissue	mature	42.965±1.272	76.371±1.792*	58.019±1.085**
	old male	46.665±1.419	81.901±0.795*	71.609±0.897**
POM, $\lambda=370$, units/g of tissue	mature	24.014±1.992	38.686±0.654*	29.329±1.128**
	old male	39.129±1.246	50.443±0.938*	44.329±0.869**
POM, $\lambda=430$, units/g of tissue	mature	20.243±0.699	28.543±0.714	24.657±0.830
	old male	34.4±0.721	48.843±0.905	36.4±0.683
kidneys				
TBA AP mcmol/g of tissue	mature	45.017 ±1.627	64.979±1.116	55.749±0.708
	old male	46.555±0.980	71.719±0.778	57.727±1.008
POM, $\lambda=370$, units/g of tissue	mature	22.357±0.718	37.786±0.823	26.143±0.781
	old male	38.457±0.596	48.343±0.976	42.5±0.896
POM, $\lambda=430$, units/g of tissue	mature	18.743±0.619	26.543±0.678	21.957±0.966
	old male	36.057±0.637	55.671±3.215	43.586±1.039

Notes: * – reliability of differences compared with the control group of rats,

** – reliability of differences compared with the group of rats with scopolamine-induced Alzheimer's disease.

Source: compiled by the authors of this study

Table 2. R/B coefficient in the hippocampus and kidneys (histochemical method for "acidic" and "basic" proteins with bromophenol blue by Mikel Calvo) of rats of different ages with scopolamine-induced Alzheimer's disease and after carbacetam administration

Organs under investigation	Age	Research groups		
		Control	Scopolamine-induced Alzheimer's disease	Scopolamine-induced Alzheimer's disease + carbacetam
hippocampus	mature	1.09±0.008	1.89±0.012	1.33±0.012
	old male	1.38±0.022	1.98±0.021	1.21±0.016
endotheliocytes of non-collapsed renal glomeruli	mature	1.04±0.012	1.38±0.019	1.18±0.014
	old male	1.18±0.014	1.68±0.024	1.47±0.021
mesangial matrix of non-collapsed renal glomeruli	mature	1.06±0.013	1.38±0.021	1.18±0.015
	old male	1.19±0.016	1.72±0.026	1.52±0.022

Source: compiled by the authors of this study

Experimental data were processed on personal computers using the EXCEL-2010 statistical program package (Microsoft Corp., USA). Statistical processing of the research results was carried out using the Student's t-test. A preliminary check of the distribution of values in the samples was carried out to confirm the adequate method of statistical assessment of the average difference between the study groups. According to the Shapiro-Wilk test [17], data on the deviation of the distribution in the samples from normal ($p > 0.05$) were obtained. Taking into account the above, the use of the Student's t-test was considered sufficient to obtain valid conclusions. To confirm the

reliability of the conclusions, the non-parametric Mann-Whitney comparison test was used in parallel, which showed similar results to calculations using the Student's t-test regarding the value of p. Therefore, $p \leq 0.05$ was considered a sufficient level of probability of differences.

RESULTS

All the biological systems are known to exist in reduction-oxidation (redox) equilibrium, balancing oxidation and reduction reactions to achieve favorable conditions for life. Disturbance of this homeostasis

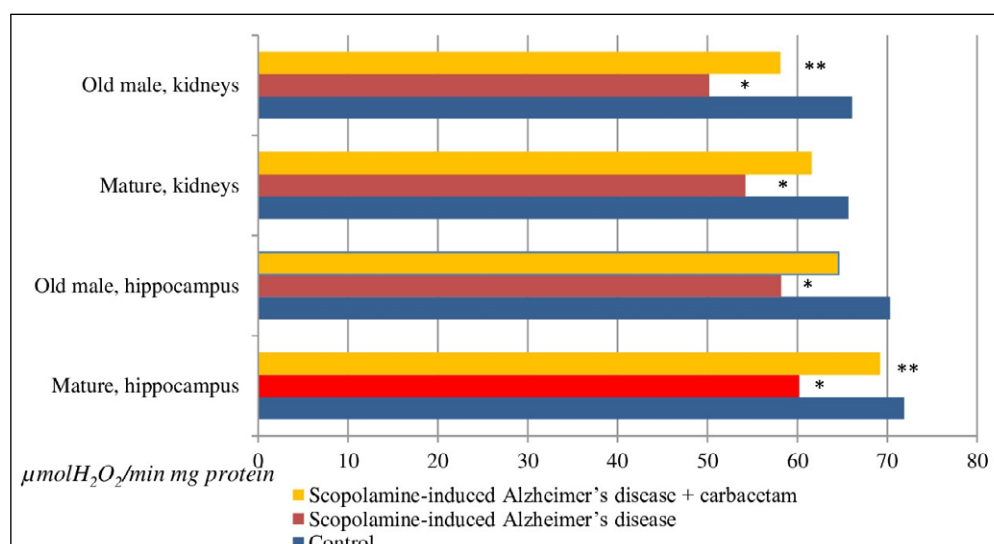


Fig. 1. Effect of carbacetam on catalase activity in the hippocampus and kidneys of rats of different ages with scopolamine-induced Alzheimer's disease, $M \pm m$

Notes: * – reliability of differences compared with the control group of rats,

** – reliability of differences compared with the group of rats with scopolamine-induced Alzheimer's disease.

Picture taken by the authors

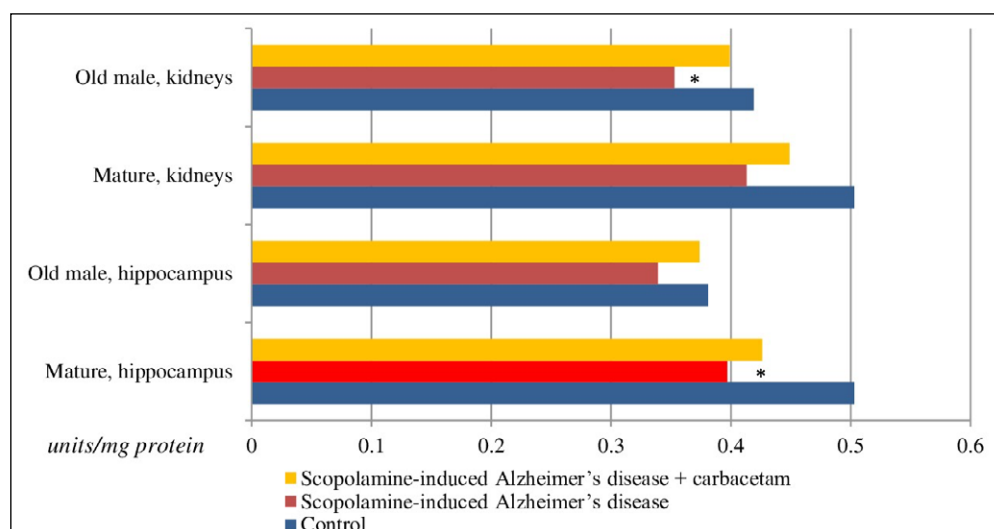


Fig. 2. Effect of carbacetam on SOD activity indices of the hippocampus and kidneys of rats of different ages with scopolamine-induced Alzheimer's disease, $M \pm m$

Notes: * – reliability of differences compared with the control group of rats,

** – reliability of differences compared with the group of rats with scopolamine-induced Alzheimer's disease

Picture taken by the authors

promotes oxidation of DNA, proteins and lipids, and thus changing their structure, activity and physical properties. Oxidation damage and reduction-oxidation equilibrium disorders are known to promote imbalance in the biological homeostasis resulting in diseases or even death. Alzheimer's disease is no exception. This pathology is characterized by progressive loss of neuronal structure and function caused by such mechanisms as oxidative stress, mitochondrial dysfunction, and chronic neuritis [18]. Oxidative damage has become a crucial factor. More and more evidences emphasize its key role in pathophysiology and advance of this pathology.

That is why the first stage of our research was to examine the state of lipid and protein peroxide oxidation in the hippocampus and kidneys of rats with an experimental model of Alzheimer-like cognitive dysfunction (Table 1). Thus, TBARS content increases both, in the hippocampus and kidneys of mature and old rats with experimental pathology. As we can

see, in the hippocampus, this indicator increased by 77.8% in sexually mature animals and by 75.5% in old ones. At the same time, an increase in the content of lipid peroxidation products was also observed in kidney homogenates. In the group of sexually mature rats TBARS content increased by 44.3%, and in old rats – by 54.1%. Thus, hippocampal lipids are more damaged. Nevertheless, against the ground of brain damage we see kidney damage as well, which is indicative of interrelationships between these examined structures.

Analyzing the results of LPO after carbacetam administration, we see a decrease in the content of TBARS in the hippocampus and kidneys of sexually mature and old rats. In particular, in the hippocampus, TBARS content decreased by 24.1% in sexually mature rats and by 14.2% in old ones, and in the kidneys by 12.6% and 19.9%, respectively.

No less significant are changes in protein peroxidation (Table 1). Thus, in the groups of sexually mature

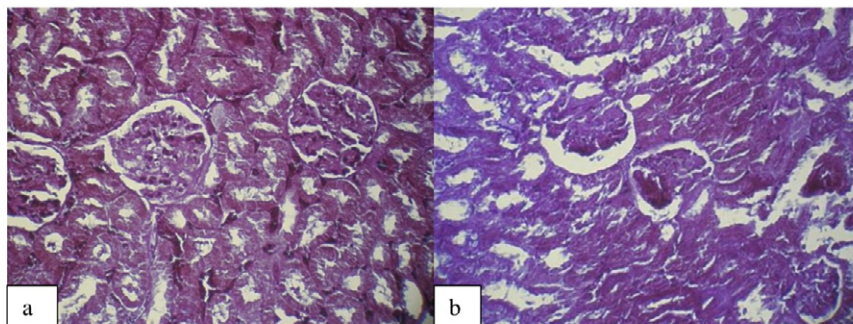


Fig. 3. R/B coefficient in endothelial cells of uncollapsed renal glomeruli of sexually mature (a), old male (b) males (when stained with bromophenol blue according to Mikel Calvo)

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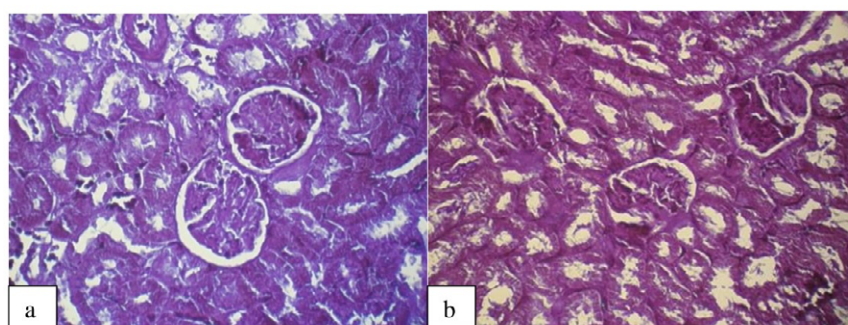


Fig. 4. R/B coefficient in endothelial cells and mesangial matrix of uncollapsed renal glomeruli of mature (a) and old male rats (b) with scopolamine-induced Alzheimer's disease (when stained with bromophenol blue according to Mikel Calvo)

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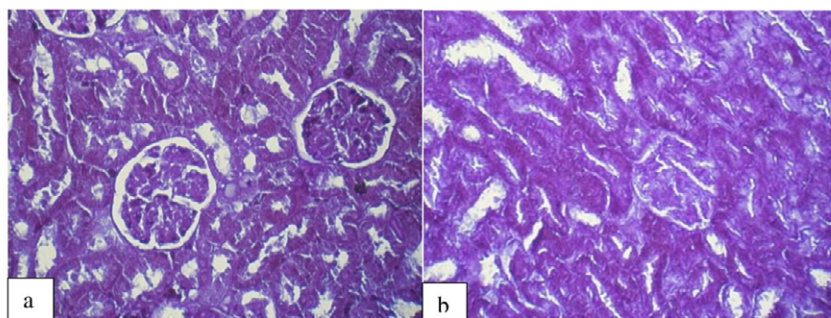


Fig. 5. R/B coefficient in endothelial cells and mesangial matrix of uncollapsed renal glomeruli of sexually mature (a) and old male (b) rats with scopolamine-induced Alzheimer's disease and upon administration of carbacetam (when stained with bromophenol blue according to Mikel Calvo).

Obj. 40x Oc. 10x

Picture taken by the authors

and old rats with a model of cognitive impairment induced by scopolamine, the content of ketone dinitrophenyl hydrozones of neutral character and aldehyde dinitrophenyl hydrozones of basic character increased in the hippocampus and kidneys. At the same time, protein content both neutral and basic by character increased in the hippocampus of sexually mature rats with model pathology by 61,1% and 41,1% respectively compared to the control group. When comparing the same indicators in the group of old rats, we observe an increase in the content of both groups of proteins: of neutral character by 28,9% and basic – by 41,9%.

The changes in the values of POM indicators in the kidneys of the examined groups were similar. In particular, the products of protein peroxide oxidation increased: those of neutral character in sexually mature rats – by 69% and basic character – by 41,6%; in the group of old rats – by 25,7% and by 54,4% respectively.

Increasing processes of protein peroxide oxidation observed in our research is one of the early markers of oxidative stress, since POM products are more stable compared to LPO metabolites, which are rapidly oxidized under the action of peroxidases. At the same time, destructuring of protein molecules can cause the damage of DNA-apparatus of cells, disturbances of

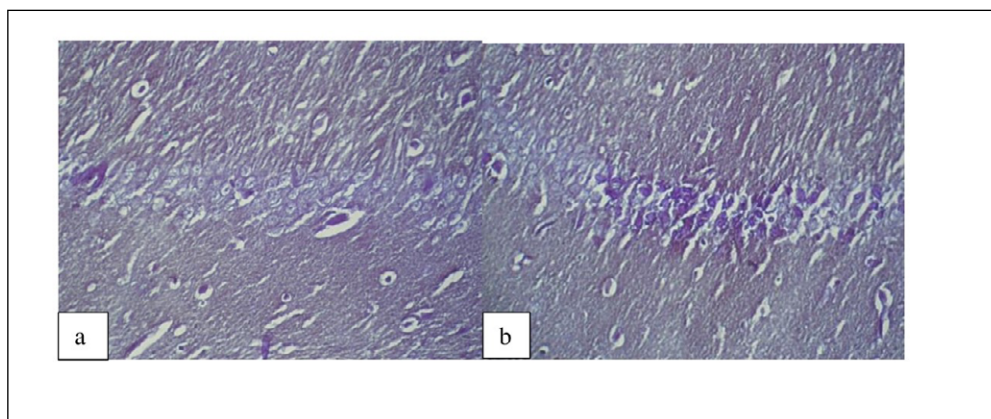


Fig. 6. R/B coefficient in hippocampal neurons of sexually mature (a) and old (b) rats (when stained with bromophenol blue according to Mikel Calvo).

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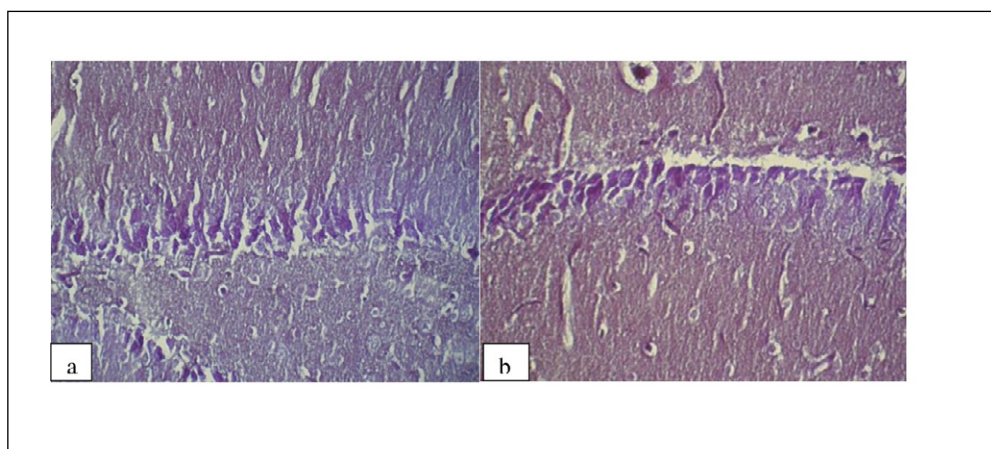


Fig. 7. R/B coefficient in hippocampal neurons of sexually mature (a) and old (b) rats with scopolamine-induced Alzheimer's disease (when stained with bromophenol blue according to Mikel Calvo).

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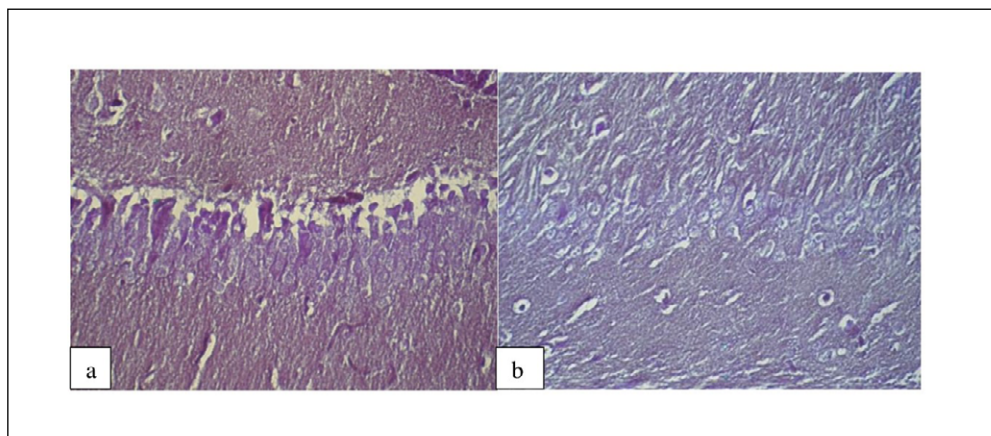


Fig. 8. R/B coefficient in hippocampal neurons of sexually mature (a) and aged (b) rats with scopolamine-induced Alzheimer's disease and carbacetam administration (when stained with bromophenol blue according to Mikel Calvo)

Obj. 40x Oc. 10x

Picture taken by the authors

respiratory and phosphorylation processes in the mitochondria, and blocking ATP synthesis [19]. Significant protein modification is a signal for changing cellular metabolism. The intensity of protein peroxidation reflects not only the degree of oxidative damage to tissues, but reserve-adaptive possibilities of the body as well [20].

14-day carbacetam administration decreased POM content in the hippocampus and kidneys of rats of different ages. Thus, in sexually mature rats, the content of ketone dinitrophenyl hydrozones of neutral character decreased by 24,2% in the hippocampus and by 30,3% in the kidneys, and the content of aldehyde dinitrophenyl hydrozones of basic character by 13,6% and 17,3% respectively. In the group of old rats, the

content of protein peroxidation products decreased as well in both examined organs. In the group of old rats, the content of ketone dinitrophenyl hydrozones of neutral character decreased by 12,1% in the hippocampus and kidneys, and the content of aldehyde dinitrophenyl hydrozones of basic character by 25,5% and 21,7% respectively.

As is known, the enzymatic activity of SOD is aimed at detoxifying superoxide anion radicals by converting them into a more stable compound - hydrogen peroxide, which is critically important for the functioning of the antioxidant system. In the hippocampus and kidneys of rats with scopolamine-induced Alzheimer's disease (Fig. 1), a decrease in the activity of this enzyme was found in

both age groups: in the hippocampus of sexually mature individuals - by 21.1%; and in the kidneys of old individuals - by 15.8%. However, when a GABA receptor modulator is administered, we observe only a tendency to increase SOD activity in sexually mature and old rats both in the hippocampus and in the kidneys.

Considering that the neutralization of hydrogen peroxide, which is formed as a result of the dismutation of the superoxide radical, is carried out by catalase, we checked the state of this enzyme in the groups of rats under study. In rats with scopolamine-induced Alzheimer's disease, catalase activity (Fig. 2) compared to the control decreased on average by 16.9% in the hippocampus and by 20.6% in the kidneys of rats of different ages. At the same time, the administration of carbacetam increased the activity of this enzyme in the hippocampus of sexually mature and kidneys of old rats by 14.8% and 15.7%, respectively. In other groups, there is a tendency to increase the activity of this enzyme. That is, the administration of carbacetam, as a GABA receptor modulator, in experimental scopolamine-induced Alzheimer's disease promotes the restoration of antioxidant protection, significantly increasing catalase activity in the hippocampus and kidneys, while SOD activity demonstrates only a positive trend towards growth.

Since POM reflects changes in the ratio between amino- and carboxyl groups, which can be estimated by means of histochemical method for "acidic" and "basic" proteins with bromophenol blue by Mikel Calvo, when proteins are stained in different colors depending on their properties according to the ratio of amino- and carboxyl groups [17]. For example, with a clear predominance of amino groups in proteins, they are stained blue, and with a clear predominance of carboxyl groups, they are stained red. In practice, combined staining always occurs due to the presence of a "mixture" of proteins in the tissues, which prompts the use of not only visual but also quantitative assessment of POM degree.

We used this method in our research as well. After processing the data obtained, we were interested in studying the quantitative assessment of the state of the hippocampal and kidney proteins in rat histochemical samples stained with bromophenol blue according to Mikel Calvo (Fig.3.a,b, Fig 6.a.b). The findings obtained in our research are in Table 2. In the group of sexually mature and old rats with a model of cognitive impairment, induced by scopolamine increasing R/B coefficient was detected both in the hippocampal neurons and endotheliocytes, and in the mesangial matrix of non-collapsed renal glomeruli by 73,4%; 43,5%; 32,7%; 42,4%; 30,2%; 44,5% respectively (Fig. 4.a, b, Fig 7.a, b). The results obtained by means of this method correlate with the findings of the biochemical examination.

In sexually mature rats with simulated pathology

that received carbacetam, the examined coefficient decreased by 29,6% and by 14,5% in the kidneys; by 14,5% in the endotheliocytes, and in the mesangial matrix of non-collapsed renal glomeruli (Fig. 5.a., Fig 5.b) In the group of old rats R/B coefficient decreased as well: in the hippocampus and kidneys by 38,9%, 12,5%, 11,6% respectively (Fig. 8.a., Fig 8.b).

Thus, when modeling scopolamine-induced Alzheimer's disease, we observe damage to the amino groups of proteins in the hippocampal neurons and in the endotheliocytes, and in the mesangial matrix of non-collapsed renal glomeruli of rats of different ages having more pronounced changes in the brain cells. At the same time, there is an existing interrelationship between damage to neurons and kidney cells, which makes a foundation for further investigation of pathogenic processes and interrelations in neurodegenerative processes.

DISCUSSION

In our opinion, the obtained data are the basis for studying the possible new functional role of GABA receptors in the mechanisms of kidney damage. However, our studies used a pharmacological model of cognitive disorders with animal studies and the mechanistic pathways involving GABA receptors were not directly studied.

However, when analyzing the obtained data, it was found that modeling scopolamine-induced Alzheimer's disease in rats of all age groups triggers a cascade of pathobiochemical reactions that initiate the development of a pronounced systemic oxidative process. This is manifested by the intensification of peroxidative damage to lipids and proteins against the background of critical suppression of the endogenous antioxidant system. During the study, a clear tissue specificity of the lesion was established, in particular, hippocampal cells show significantly higher vulnerability to free radical damage compared to kidney tissues. This selectivity of neuronal damage directly correlates with a deeper depletion of the enzymatic reserve in the nervous tissue, which is probably due to the high density of GABAergic receptors, intense oxygen consumption, and relatively low levels of protective enzymes in the hippocampus [21].

At the same time, the use of carbacetam as a positive modulator of GABA receptors opens up new prospects for the correction of these disorders. Presumably, activation of GABAergic signaling contributes to the restoration of excitatory-inhibitory balance[22], which limits the phenomena of excitotoxicity and secondary oxidative stress. Based on the conducted study, a relationship was recorded between the neuroprotective

effect of the drug and its ability to modulate the activity of key antioxidant enzymes - SOD and catalase.

Of particular interest are parallel changes in enzymatic activity in the hippocampus and kidneys. The ability of carbaracetam to reduce the amount of oxidation products in both types of tissues indicates the involvement of the GABAergic system in the common mechanisms of neuro- and renoprotection. This suggests that the drug not only locally protects the hippocampus from atrophy [21], but also has a systemic detoxification effect, supporting the functional state of the kidneys as a key organ for the elimination of metabolites [23].

However, based on a review of the literature, it is possible to hypothesize a possible brain-kidney interaction that is critical for maintaining homeostasis. For example, according to [20], a decrease in GABA receptor activity leads to activation of the renin-angiotensin-aldosterone system, which stimulates NADPH oxidase, which leads to excessive production of reactive oxygen species and the development of a systemic prooxidant state. In this case, systemic inflammatory markers and reactive oxygen species resulting from renal dysfunction increase the permeability of the blood-brain barrier. At the same time, prooxidants reduce the activity of glutamate decarboxylase, which is involved in the synthesis of GABA in the brain [24]. As a result, the excitation/inhibition balance is disturbed with an increase in

neurodegeneration or cognitive deficit. That is, a "vicious circle" is formed.

Thus, the obtained data confirm that the limitation of systemic oxidative stress under the influence of carbaracetam is a pathogenetically justified basis for its further study as a means of complex therapy of neurodegenerative disorders, regardless of the age factor. It also acts as a new potentially effective direction of preventive therapy and treatment of kidney diseases.

CONCLUSIONS

1. Modeling scopolamine-induced Alzheimer's disease leads to the development of pronounced oxidative stress in the hippocampus and kidneys of rats of all age groups, which is manifested by the intensification of peroxidative damage to lipids and proteins and the suppression of antioxidant defense mechanisms.
2. The tissue specificity of the pathological process has been established: hippocampal cells exhibit higher vulnerability to free radical damage compared to kidney tissues, which correlates with a deeper suppression of the enzymatic link of antioxidant defense in nervous tissue.
3. The ability of carbaracetam to reduce the amount of oxidation products indicates the involvement of the GABAergic system in the mechanisms of neuro- and renoprotection, which is the basis for further study of their feasibility in neurodegenerative disorders.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Yevhen P. Dreznal

Bukovinian State Medical University
2 Teatralna Square, 58002 Chernivtsi, Ukraine
e-mail: dreznal555@gmail.com

ORCID AND CONTRIBUTIONSHIP

Yevhen P. Dreznal: 0009-0004-2141-1498 [A](#) [B](#) [C](#) [D](#)
 Taras I. Kmet: 0000-0002-2850-9111 [A](#) [F](#)
 Igor Sv. Davydenko: 0000-0001-6712-3396 [B](#) [F](#)
 Ksenia V. Slobodian: 0000-0001-7872-6731 [E](#)
 Oksana V. Kushnir: 0000-0003-1472-9137 [B](#)
 Khrystyna I. Pudiak: 0000-0002-0157-1433 [A](#)

[A](#) – Work concept and design, [B](#) – Data collection and analysis, [C](#) – Responsibility for statistical analysis, [D](#) – Writing the article, [E](#) – Critical review, [F](#) – Final approval of the article

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