Experimental study

Choroidal, retinal and optic nerve ultrastructure in a rat model of chronic alcohol intoxication

Molchaniuk N. I. [1], Gushcha S. G. [2], Nasibullin B. A.[2]

[1] SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine", Odesa (Ukraine)
[2] State Non-profit Enterprise "Ukrainian Research Institute of Rehabilitation and Balneology of the Ministry of Health of Ukraine", Odesa (Ukraine)

Ультраструктура хоріоідеї, сітківки та зорового нерва щурів за умов моделювання хронічної алкогольної інтоксикації

Молчанюк Н. І.[1], Гуща С. Г. [2], Насібуллін Б. А. [2]

[1] ДУ «Інститут очних хвороб і тканинної терапії ім. В.П. Філатова НАМН України», Одеса (Україна)
[2] Державне некомерційне товариство «Український науково-дослідний інститут реабілітації та курортології МОЗ України», Одеса (Україна)

Abstract

Purpose. *To assess ultrastructural choroidal, retinal and optic nerve changes in a 45-day rat model of chronic alcohol intoxication (CAI).*

Material and Methods. *Transmission electron microscopy was used to examine the ultrastructural choroidal, retinal and optic nerve changes in a 45-day rat model of CAI which was induced in group 1, the examination group of animals, by daily intragastric injections of 25% ethanol at a dose of 1.5% of the body weight (4.0 g of 96% ethanol/kg/day). Group 2, the control group, received a 45-day course of injection water intragastric in the same volume as ethanol.*

Results. *CAI was found to cause complex lesions in all examined ocular tissues. The choroid was edematous and exhibited microvascular endothelial destruction, the absence of fenestrations and basal membrane thickening in endothelial cells. In the retina, photoreceptor cells were the most vulnerable, exhibiting vesiculation of the membranes of outer segment discs, cell fragmentation and destruction. The optic nerve exhibited glial cell destruction, nerve fiber demyelination, myelin sheath splitting, and destroyed neurofilaments and neurotubules in the axoplasm.*

Conclusion. *In rats, CAI causes systemic alcohol-induced ocular posterior segment lesions which are driven by impaired microcirculation and membrane-destructive processes.*

Keywords: *choroid, choriocapillaries, retina, photoreceptor cells, optic nerve, chronic alcohol intoxication, ultrastructure.*

Резюме

Мета. *Вивчити характер ультраструктурних змін у хоріоідеї, сітківці та зоровому нерві щурів після моделювання 45-денної хронічної алкогольної інтоксикації (ХАІ).*

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Corresponding author: Molchaniuk N.I., Cand Sc (Biol) and Senior Researcher. E-mail: elmicroscop@gmail.com

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Матеріал та методи. *За допомогою трансмісійного електронного мікроскопу вивчено ультраструктурні зміни в хоріоідеї, сітківці та зоровому нерві щурів лінії вістар після 45-денної ХАІ, яка відтворювалася шляхом щоденного внутрішньошлункового введення щурам через стравохід 25% розчину етанолу в дозі 1,5% від маси тіла, що відповідало 4 г 96% етанолу на 1 кг маси тіла тварини (піддослідна група). Контролем слугували вищевказані тканини щурів, яким упродовж 45 днів вводили воду для ін'єкцій через стравохід в аналогічному об'ємі, що і етиловий спирт.*

Результати. *Встановлено, що ХАІ спричиняє комплексне ураження всіх досліджуваних тканин ока. У хоріоідеї виявлено набряк та деструкцію ендотелію мікросудин, втрату фенестрації та потовщення їх базальних мембран. У сітківці найбільш вразливими виявилися фоторецепторні клітини, в яких визначалася везикуляція дисків зовнішніх сегментів, фрагментація та деструкція їхніх клітинних елементів. У зоровому нерві відмічено деструкцію гліальних клітин, демієлінізацію та розшарування мієлінових оболонок нервових волокон, руйнування нейрофіламентів та нейротрубочок в аксоплазмі.*

Висновок. *ХАІ викликає системний характер алкогольіндукованого ураження структур заднього відділу очей щурів в основі якого лежать порушення мікроциркуляції та мембранодеструктивні процеси.*

Ключові слова: *хоріоідея, хоріокапіляри, сітківка, фоторецепторні клітини, зоровий нерв, хронічна алкогольна інтоксикація, ультраструктура.*

Introduction

Chronic alcohol intoxication (CAI) is still a major medical and social concern which affects practically all countries regardless of their level of economic development. According to the World Health Organization (WHO), alcohol consumption contributes to 2.6 million deaths each year globally and overall, harmful use of alcohol is responsible for 4.7% of the global burden of disease. The issue is especially pressing in Ukraine due to the prevalence of systematic consumption of strong alcohol beverages and a lack of public awareness of the health (and, particularly, visual system) consequences of chronic alcohol abuse [1].

Various pathogenetic mechanisms mediate the toxic effects of methanol and its metabolites on the body. Acetaldehyde, a major metabolic product of ethanol, is a highly reactive compound capable of covalently binding to proteins, lipids and nucleic acids, causing a loss of structural and functional integrity in cell membranes and enzyme systems and cell's genetic apparatus [2, 3]. Alcohol metabolism-mediated oxidative stress is also a major mechanism of alcohol-induced tissue injury, with chronic alcohol use resulting in oxidative stress through increased metabolism via the cytochrome P450 2E1 system producing reactive oxygen species, which leads to intensified cell membrane lipid peroxidation [4]. Chronic ethanol consumption results in poor mitochondrial metabolism with inhibition of oxidative phosphorylation and adenosine triphosphate deficiency, creating the conditions for the development of energy deficiency and cell death [5, 6, 7, 8].

The impact of chronic alcohol consumption on the central nervous system (CNS) has been examined quite thoroughly. Durable use of ethanol results in neurodegenerative changes in the cortex, cerebellum, hippocampus and other CNS structures, which is associated with impaired cognitive and memory function and motor coordination [7]. At the subcellular level, alcohol-induced neurotoxication manifests as nerve fiber demyelination, destruction of synaptic contacts, neuronal perikaryon swelling, and mitochondrial alteration [9]. Recently, neuroinflammation has been increasingly identified as playing a pathogenic role in alcohol-induced neurodegeneration: chronic ethanol exposure activates microglia and astrocytes with subsequent release of pro-inflammatory cytokines, exacerbating damage to the neural tissue [6, 10].

The impact of chronic alcohol consumption on visual system structures is much less studied than on the CNS, although clinical observations show a high incidence of ophthalmological complications in individuals with alcohol addiction. Alcohol-induced optic neuropathy with a gradual decrease in vision, loss of color perception and the presence of central scotoma has been described [9, 11]. Chronic alcohol consumption affects the retina, and patients with alcohol addiction had optical coherence tomography (OCT) evidence of retinal nerve fiber layer (RNFL) thinning [12]. Animal studies have demonstrated that ethanol can induce apoptosis of retinal ganglion cells through caspase-3 activation and accumulation of reactive oxygen species [5].

Although it is the choriocapillaris that nourishes the retinal pigment epithelium (RPE) and photoreceptors, the impact of alcohol on the choroid has been very poorly studied. Optic nerve susceptibility to alcohol-induced damage has been documented experimentally and clinically. Toxic effects of ethanol on the optic nerve are implemented directly through axonal and myelin sheath damage, and indirectly through abnormalities in microcirculation and oxidative stress [13]. Unidirectional changes in the optic nerve have been reported after a single exposure to a 3:1 ethanol-methanol mixture [14].

Despite the accumulated data on the effects of alcohol exposure on individual structures of the visual system, comprehensive ultrastructural studies of an entire choroid, retina and optic nerve pathway have been insufficiently reported. Such a systematic approach would enable assessing the severity and sequence of structural changes throughout the pathway including visual system

components, and determining those most susceptible to the toxic effects of ethanol.

The purpose of the study was to assess ultrastructural choroidal, retinal and optic nerve changes in a 45-day rat model of chronic alcohol intoxication.

Material and Methods

Five adult white Wistar rats (10 eyes) were used in the experiment. Animals were divided into two groups. In group 1, the experimental group, chronic alcoholization was induced by intraperitoneal injections of 25% ethanol at a dose of 1.5% of the body weight (4.0 g of 96% ethanol/kg/day) during 45 days. Group 2 received a 45-day course of injection water in the same volume as ethanol. Choroidal, retinal and optic nerve structures were examined by electron microscopy. Animals were euthanized with sodium thiopental, in accordance with the provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 1986). The article was approved by the Bioethics Committee of 1SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine" on April 16, 2026.

Tissue specimens were fixed in 2.5% glutaraldehyde in phosphate buffer (pH 7.4), postfixed in 1% osmium tetroxide (OsO4), dehydrated in a gradient series of ethanol and propylene oxide, embedded in an Epon–Araldite mixture, and observed with a PEM-100-01 Transmission Electron Microscope (Selmi, Sumy, Ukraine). This study is qualitative and does not include statistical analysis.

Results

We found ultrastructural evidence of clear cytoplasmic zones in the endothelial cells in choroidal microvessels, indicating the development of cellular swelling. In the cytoplasm of these cells, organelles were decreased in number, with some of them showing signs of destruction. In endothelial cells, the structure of the nucleus appeared better preserved than the structure of cytoplasmic organelles. A portion of vessels had narrowed lumens, with erythrocytes infrequently found within the latter. Lumen contents were characteristic of significantly homogeneous plasma and its increased electron density. A characteristic feature was the loss of fenestrations in the endothelial cell lining of choriocapillaries and thickening of the endothelial cell basal membrane. Membranes and organelles in these cells appeared fuzzy. Interstitial tissue appeared saturated with protein plasma and almost homogeneous and osmiophilic at some sites and, on the contrary, showed signs of edema at other sites.

RPE cells exhibited polymorphic changes. Some cells showed an almost normal structure, whereas other, alterations and destructive changes in organelles. Of note were increased numbers of phagosomes in the apical RPE, which reflected intensified phagocytosis of damaged fragments of the outer segments (OS) of photoreceptor cells (PC). There were distinct areas of photoreceptor outer-segment separation from the RPE, with signs of destruction being more marked in membranous organelles in these RPE cells than in other RPE cells (Figs 1, 2).

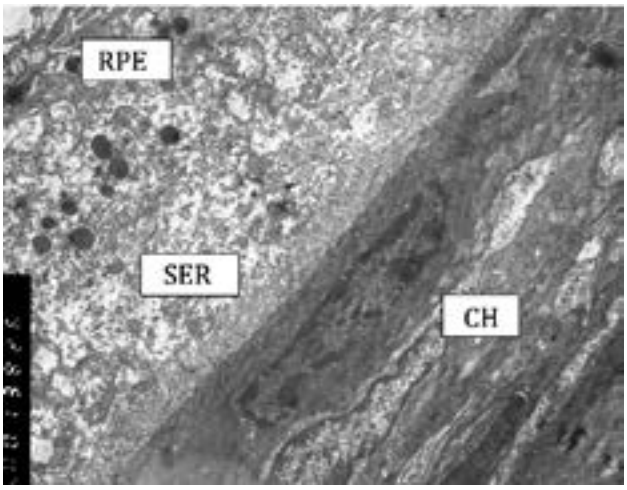

Fig. 1. Electron micrograph showing ultrastructure of the chorioretinal complex after a 45-day course of injection water. The structure of the choriocapillaries and a retinal pigment epithelium cell appear normal. Original magnification ×5,000. Notes: CH, choriocapillaries; RPE, retinal pigment epithelium; SER, smooth endoplasmic reticulum

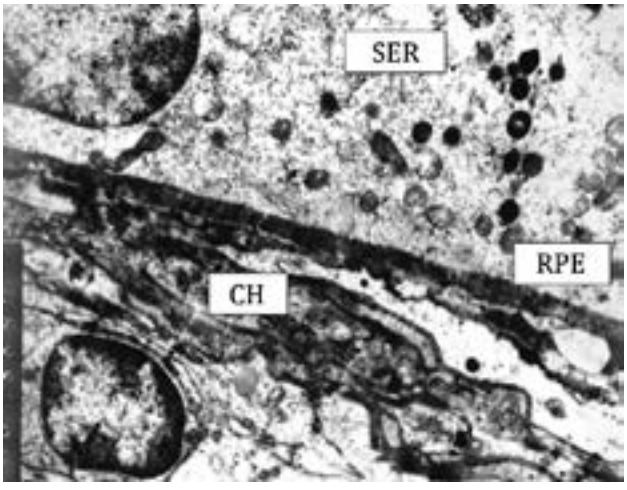

Fig. 2. Electron micrograph showing ultrastructure of the chorioretinal complex after chronic intoxication with ethanol. The lumens of microvessels appear narrow, basal membranes thickened and dilated, and there is loss of vascular wall fenestration. There is alteration of smooth endoplasmic reticulum vesicles which appear sparsely spaced. Notes: CH, choriocapillaries; RPE, retinal pigment epithelium; SER, smooth endoplasmic reticulum.

In the interphotoreceptor matrix, there were large numbers of PCOS fragments at various stages of degradation. Vesiculation of the membranes of PCOS discs was especially marked. PCOS and PC inner segments (IS) were disorganized, fragmented and destroyed, and their numbers were notably small. The outer limiting membrane appeared preserved. Additionally, PC showed significant damage to intracellular cytoplasmic structures. The perinuclear region and nucleus in PC were compressed by edema (Figs 3, 4).

Substantial cellular swelling was observed in the bipolar cell region. In the RNFL, only some portion of retinal nerve fibers appeared swollen. Retinal vessels appeared satisfactory. Hydropic and degenerative changes in ganglion cells were seen (Figs 5, 6).

Optic nerve glial cells showed various degrees of destruction from cells with a relatively typical structure and signs of alteration to cytoplasmic depletion with an electron-transparent space filled with fragments of membrane structures and altered nucleus (Figs 7, 8).

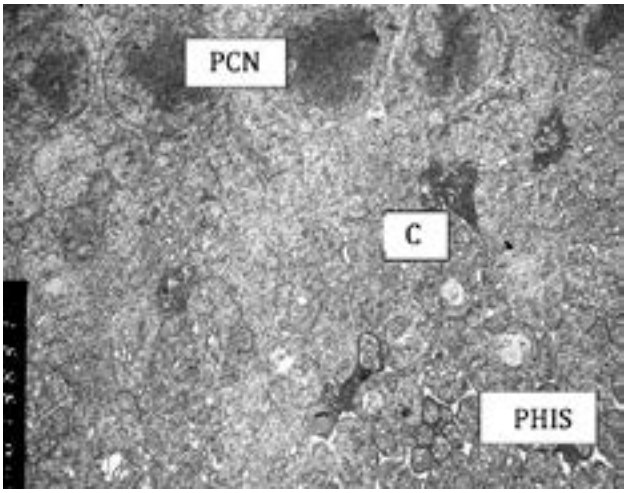

Fig. 3. Electron micrograph showing ultrastructure of the rat retina after a 45-day course of injection water. Structural components of photoreceptor cells appear normal. Original magnification ×6,000. Notes: C, cytoplasm; PCN, nuclei of photoreceptor cells; PHIS, photoreceptor inner segments.

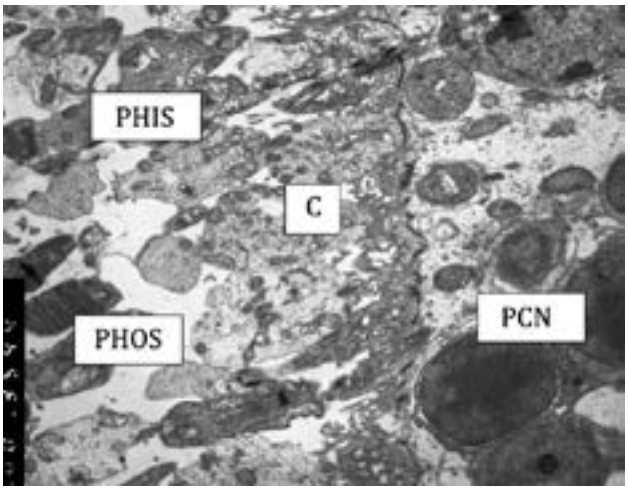

Fig. 4. Electron micrograph showing ultrastructure of the rat retina after chronic intoxication with ethanol. There are intercellular swelling and disorganization and alteration of the inner and outer segments and cytoplasm of photoreceptor cells. Original magnification ×4,000. Notes: C, cytoplasm; PCN, nuclei of photoreceptor cells; PHIS, photoreceptor inner segments; PHOS, photoreceptor outer segments.

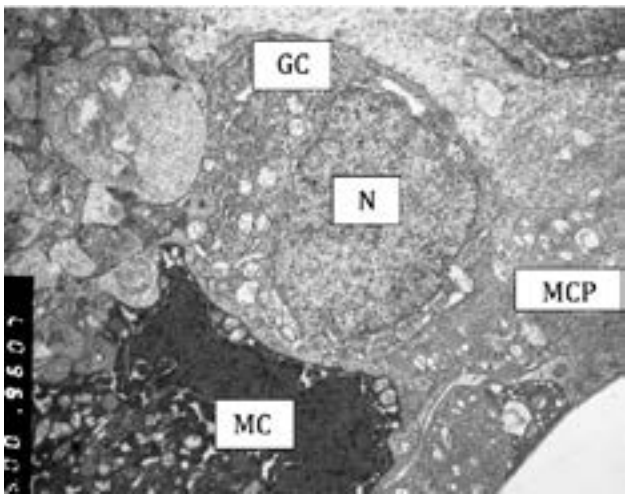

Fig. 5. Electron micrograph showing ultrastructure of the rat retina after a 45-day course of injection water. The ganglion cell and Műller cell processes exhibit metabolic activity. The microglial cell is at rest. Original magnification ×4,000. Notes: GC, ganglion cell; MC, microglial cell; MCP, Műller cell processes; N, nucleus.

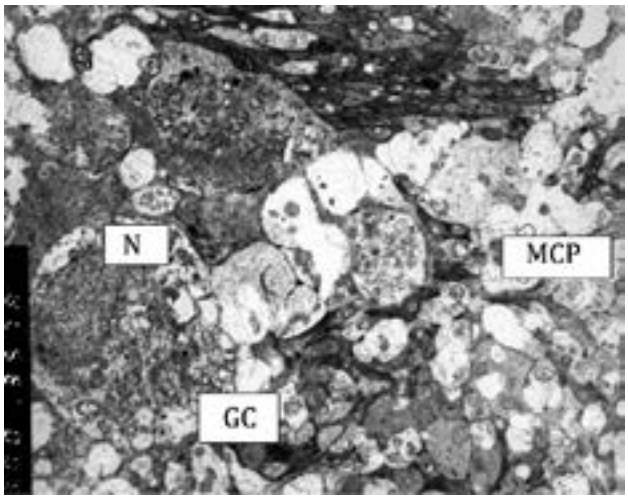

Fig. 6. Electron micrograph showing ultrastructure of the rat retina after chronic intoxication with ethanol. Swelling and destruction of organelles in the ganglion cell and Műller cell processes can be seen. Original magnification ×4,000. Notes: GC, ganglion cell; MCP, Műller cell processes; N, nucleus.

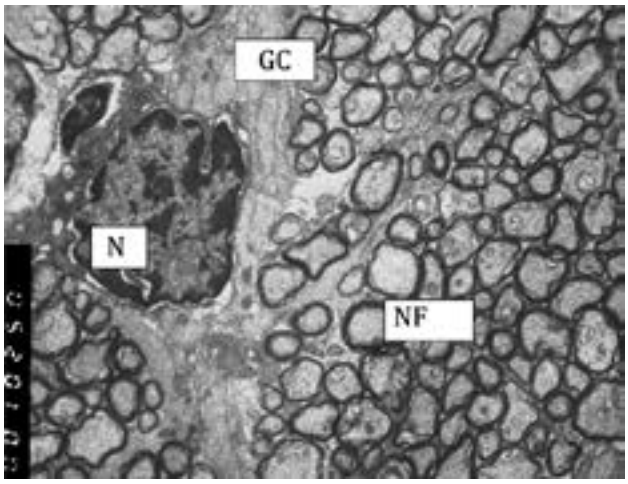

Fig. 7. Electron micrograph showing ultrastructure of the rat's optic nerve after a 45-day course of injection water. Neural filaments and the glial cell appear normal. Original magnification ×4,000. Notes: GC, glial cell; N, nucleus; NF, neural filaments.

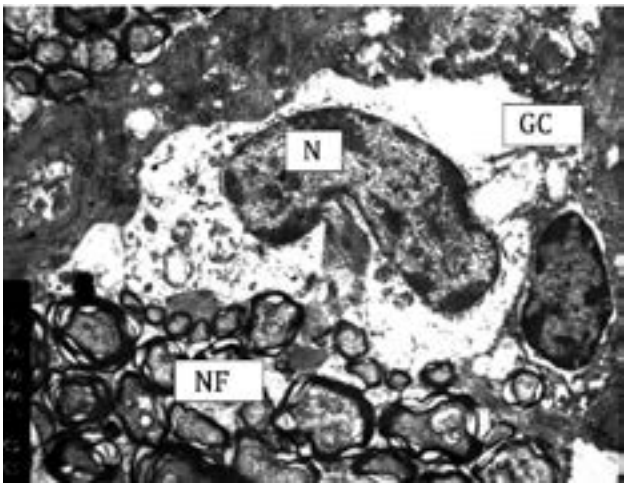

Fig. 8. Electron micrograph showing ultrastructure of the rat's optic nerve after chronic intoxication with ethanol. The glial cell appears destroyed and myelin sheath splitting can be seen in the optic nerve. Original magnification ×6,000. Notes: GC, glial cell; N, nucleus; NF, neural filaments.

In the optic nerve fibers, there were areas of homogeneous osmiophilic myelin sheaths, lamellar fusion and sheath splitting. The axoplasm was more preserved in some neural fibers. In other neural fibers, however, it appeared swollen, while axoplasmic neurofilaments and microtubules appeared fuzzy, dense and homogeneous or their number was less than normal. Optic nerve lesions in CAI serve a morphological basis for toxic optic neuropathy, a syndrome characterized by progressive visual acuity loss in chronic alcohol addicts [11, 15].

Discussion

Our ultrastructural study found a combination of pathological changes in all examined rat tissues after 45-day CAI with a 25% ethanol solution.

The changes found in the choroid morphologically reflect abnormalities in microhemocirculation caused by a toxic effect of ethanol and its metabolites on the vascular bed endothelium. Acetaldehyde is a primary product of ethanol oxidation by alcohol dehydrogenase, a highly reactive compound capable of forming covalent adducts with proteins and lipids of cellular membranes, which impairs their structural integrity [16, 17].

Chriocapillaris fenestration loss and basal membrane thickening are very unfavorable signs, because it is through endothelial fenestrations that nutrients and oxygen are transported to the outer retina. An impairment of this transport creates the conditions for the development of chronic ischemia in the RPE and photoreceptor layer. Another factor of endothelial damage is oxidative stress caused by the induction of the P450 2E1 enzyme by chronic exposure to ethanol, the process that has been studied in detail in a model of alcohol-induced liver injury [2, 4] and characteristic of all the tissues that metabolize ethanol. Chronic alcohol consumption also causes an impairment of mitochondrial metabolism with inhibition of oxidative phosphorylation and the induction of cell energy deficiency, which is a universal mechanism of alcohol-induced cytotoxicity [8, 19]. Our findings for the first time demonstrate that even a moderate-term CAI can induce severe ultrastructural changes in the retina, particularly, in the choriocapillary bed, which confirms a systemic nature of alcohol-induced microangiopathy.

Damage to the photoreceptor apparatus is a major retinal consequence of CAI, because it directly determines the severity of damage to visual function. Vesiculation of OS disc membranes and cell fragmentation which we found may be associated with a direct membrane-toxic effect of acetaldehyde and lipid peroxidation products [17, 20], or/and ischemia secondary to abnormal choroidal blood supply described above. Experimental studies on animal models have demonstrated that ethanol can induce apoptosis of retinal ganglion neuronal cells, with this process mediated by excessive accumulation of reactive oxygen species and caspase-3 activation [5, 21]. Our findings of hydropic changes in ganglion cells and swelling of a portion of nerve fibers are in agreement with the results of clinical studies which reported on the OCT evidence of RNFL thinning in patients with chronic alcoholism [12]. Other studies reported similar data on RNFL thinning in alcohol-induced toxic optic neuropathy [20]. An abnormal accumulation of phagosomes in RPE cells indicates an increased load on the system for digestion of outer segment disc fragments, which in the presence of long-term alcoholization may result in functional depletion of RPE cells with subsequent RPE decompensation.

It is noteworthy that, in the current study, intraretinal vessels, but not choriocapillaries, have preserved a relatively satisfactory ultrastructure, which confirms

a predominantly external (choroidal) origin of retinal ischemic damage in CAI.

Additionally, out finding of various glial changes ranging from moderate alterations in organelles to cytoplasmic depletion reflects different sensitivities of individual glial cells to toxic exposure and, possibly, different durations of their exposure to metabolic stress. Such a variation in glial cell response to chronic alcohol exposure has been described for other CNS compartments, where microglial and astrocyte activation was accompanied by pro-inflammatory cytokine release, exacerbating the neurodegenetative process [10, 22]. Nerve fiber demyelination with myelin sheath splitting or homogenization is a classic manifestation of alcoholic neuropathy [23]. The mechanism of demyelination is associated with direct membranolytic effects of ethanol on the lipid components of myelin [23, 17] and an abnormal trophic function of oligodendrocytes resulting from mitochondrial dysfunction [19]. The breakdown of axoplasmic neurofilaments and microtubules indicates severe abnormalities in the cytoskeletal organization of axons, which inevitably results in disorganization of axoplasic transport and nerve fiber dysfunction. Experimental studies have demonstrated that alcohol-induced intoxication is underpinned by a set of interrelated mechanisms including oxidative stress, neuroinflammation and impaired neurogenesis, which has been [15, 24]. Alcohol-induced damage to neurons at different CNS levels (including the cortex and cerebellum) is accompanied by demyelination, neuronal death and reactive gliosis [7, 24, 25]. The combination of myelinopathy and axonopathy determines the severity and, to a large extent, irreversibility of optic nerve damage in chronic alcoholism.

Therefore, the results of the present study demonstrate that 45-day CAI with a 25% ethanol solution caused a systemic damage to the entire complex of the examined tissues. The pathological process involving the choroid affects microhemocirculation, the barrier function of choriocapillaris, and all retinal cell layers, with predominant damage to the photoreceptor apparatus and optic disc, and the development of myelinopathy and axonopathy, in the presence of glial destruction. The ultrastructural changes found were consistent with the general biochemical mechanisms of alcohol cytotoxicity (mitochondrial metabolic abnormality and cell energy deficiency [19], membrane destruction due to oxidative stress [4, 17] and neuroimmune activation with pro-inflammatory cytokine production [3]) which had been studied in detail in various models of chronic alcoholization. The above findings were also confirmed by several studies [19]. Others found abnormal ocular and brain hemodynamics in patients with acute or long-term optic neuritis and those with complications of the disease [26].

The above negative effects of alcohol intoxication result not only in tissue lesions in the visual system, but also in those in other organs such as the brain, heart, liver, and kidney, which is accompanied by reorganization of the activity of functional systems, exhaustion of regulating mechanisms, and impairment of antioxidative defense [27, 28, 29]. This requires a systemic correction of an imbalance in the activity of functional systems. Under any conditions, especially in the presence of pathological process, it is required to maintain the balance of functional systems, because failure to maintain the balance may result in dysfunction. Consequently, studies are warranted to investigate correlations among structural and functional changes in different functional systems of the body (e.g., the visual system, brain, liver, heart and kidneys) in CAI.

Therefore, a 45-day CAI with 25% ethanol solution caused marked ultrastructural changes in the choriocapillary endothelium, which is manifested by cellular swelling, organelle destruction, loss of vascular wall fenestration and basal membrane thickening, creating the conditions for the development of chronic ischemia of the outer retina. In the retina, the most susceptible to alcohol-induced damage is the photoreceptor apparatus: we found massive vesiculation of OS disc membranes, PC fragmentation and destruction, compression of PC nucleus from swelling, and an abnormal accumulation of phagosomes in RPE cells, which indicates intensified phagocytosis of fragments of photoreceptor outer segment discs. Ultrastructural changes in the optic nerve are characterized by various alterations in glial cells (from damage to individual organelles to total loss of organelles), demyelination or splitting and homogenization of myelin sheaths of nerve fibers, and destruction of axoplasmic microtubules and neurofilaments, which indicates the development of myelinopathy combined with axonopathy.

In total, the ultrastructural changes found in the choroid, retina and optic nerve pathway indicate a systemic nature of lesions in the examined tissues in CAI, which are driven by impaired microcirculation in the choriocapillaris bed, and membrane destruction and mitochondrial dysfunction in the examined structures caused by direct and indirect effects of ethanol and its metabolites.

Author Contributions

NM: Conceptualization, Study Design, Experimental Investigation, Data Analysis and Interpretation, Conclusion Formulation; SG: Data Collection, Experimental Investigation, Data Analysis and Interpretation, Writing—review & editing; BN: Writing—review & editing. All authors reviewed the results and approved the final version of the manuscript.

Disclaimers

The opinions presented in this article are those of the authors and do not necessarily represent those of their institutions.

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Conflict of Interest

The authors declare that they have no actual or potential conflict of interest that could inappropriately influence, or be perceived to influence, the subject matter or material discussed in this manuscript.

Study objects

Rat retina and optic nerve. Animals were maintained in accordance with the institutional and national standards for the care and use of laboratory animals. Animal experiments and euthanasia were performed in accordance with the provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 1986). The article was approved by the Bioethics Committee of 1SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine" on April 16, 2026.

Data Availability Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Abbreviations

CAI, chronic alcohol intoxication; CNS, central nervous system; IS, inner segments; ON, optic nerve; OS, outer segments; PC, photoreceptor cells; RPE, retinal pigment epithelium

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