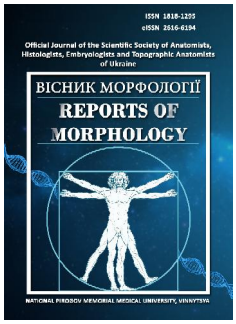
DOI: 10.31393/morphology-journal-2021-27(3)-07 Reports of Morphology, Vol. 27, №3, Pages 49-54

ISSN 1818-1295 eISSN 2616-6194

REPORTS OF MORPHOLOGY

*Official Journal of the Scientific Society of Anatomists, Histologists, Embryologists and Topographic Anatomists of Ukraine*

journal homepage: https://morphology-journal.com




# Dynamics of ultrastructural changes in glial cells and nerve fibers of the optic nerve of rats after intra-abdominal injection of a mixture of 40% Ethanol solution and 100% Methanol

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**ARTICLE INFO**

Received: 20 July 2021

Accepted: 20 August 2021

**UDC:** 617.723./.35:615.032.-578.089.821-547.42-092.19

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*There are, quite often, cases of poisoning of human population with poor-quality alcoholic drinks, which include methanol. The optic nerve, retina and brain tissues are initially affected. A long-term study aimed at identifying initial structural changes in the visual analyzer in the application of various doses of methanol and its mixture with ethanol was carried out. Purpose: to study the dynamics of ultrastructural changes in glial cells and nerve fibers of the optic nerve, which are caused by mixture of ethanol 40% and methanol 100% in a ratio of 3:1 with a dose of methanol of 0.75 g/kg of rat weight. We examined the ultrastructure of the orbit part of the optic nerve of 43 adult rats (Wistar line) in the period from 3 hours to 14 days after one-time intra-abdominal injection of ethanol 40% and methanol 100%, 100% methanol, the dose of methanol is 0.75 g/kg of rat weight. In rats, LD50 is 9.5 g/kg of their weight. It was found out, that within 3 hours after the injection of the mixture of alcohols, the myelin sheath of large-caliber nerve fibers exfoliated, the axoplasm swelled and the mitochondria in their axons pathologically changed, the mitochondria altered in glial cells, which influenced the quality of nerve impulses and axoplasmic transport of substances. In the dynamics of the study, alterative changes in structures of the optic nerve progressed with the complete destruction of part of glial cells by 7 days, mainly in the first 3 days. After the use of methanol 100%, changes in structures of the optic nerve were similar to changes in them after the use of a mixture of alcohols, but with more significant pathology at all periods of observation with the peak of their manifestation on the 7th day. In glial cells and axons of nerve fibers from the 1st day of the study, signs of compensatory and restorative processes were found: they increased protein-synthesizing and energy-forming functions that were aimed at restoring the damaged ultrastructure. It is established, that 3 hours after the injection of a mixture of alcohols, reactive changes in the structures of the optic nerve of rats took place, which from the 1st day develop into pathological changes and are observed up to 14 days with the peak of their activity on the 7th day of the study. After the use of methanol 100%, the ultrastructure of the optic nerve of rats is more damaged than after the injection of a mixture of alcohols. It is proved, that methanol has a leading place in the development of pathological changes in structures of the optic nerve after the injection of a mixture of alcohols.*

**Keywords:** *ultrastructure, glial cells, nerve fibers, optic nerve, mixture of alcohols, ethanol, methanol.*

## Introduction

Recently, methanol, which is a highly toxic alcohol, is being introduced into many spheres of life, in particular, for the production of low-quality alcoholic beverages. When using methanol up to 10 ml, blindness occurs, and when using it in a dose of 30-50 ml - death. In this regard, it is important to study the initial ultrastructural changes in the toxic effects of methanol on organs and systems of the human body in order to invent effective and targeted methods of treatment of its victims.

It is known that methanol primarily affects the optic nerve (ON), retina and brain tissue [2, 4, 8, 12, 14, 17, 18, 28]. In addition, acute methanol poisoning can also cause hemorrhage in the brain [2]. According to clinical data [21, 24, 27] in acute methanol poisoning there is optic nerve

neuropathy. Studies in rats have shown that methanol poisoning in ON damages nerve fibers (NF), disrupts axoplasmic circulation due to blockade of energy-producing processes associated with mitochondrial pathology [1, 7, 20, 22]. We previously found that a single intra-abdominal injection of rats 100% methanol at a dose of 0.75 g/kg body weight, which is 10 part of the lethal dose, causes in ON, primarily changes in the myelin sheaths of nerve fibers of large caliber already in the first hours of observation [6]. Studies by other authors, which were devoted to the study of electrophysiological parameters and ultrastructure of the visual analyzer of rats after methanol poisoning at a dose of 1.8 g/kg body weight, revealed significant dystrophic-degenerative changes in the structures of the retina, optic nerve and occipital cortex [23].

It is known that ethanol is an antidote to methanol and is actively used in the clinic in detoxification of victims of low-quality alcoholic beverages containing methanol, as ethanol can compete with methanol for binding to the enzyme alcohol dehydrogenase, which metabolizes alcohols [10, 16]. According to the authors [9] in white mice, methanol and ethanol have different pathways of penetration into cells through cell membranes, and ethanol has a stronger effect on the structural properties of membranes and the transport of substances from the gastrointestinal tract into the bloodstream. At the same time, in the literature there are reports [26] that in white rats ethanol, when used as an antidote for acute methanol intoxication (1.0 LD50), causes increased immunotoxic effects. Immunotoxic effects have also been found in acute ethanol poisoning [25].

In people with acute poisoning by 40% ethyl alcohol, or with its chronic use, pathological changes of internal organs are often observed [11, 15]. After conducting a series of experiments on monkeys J.Bouskila and co-authors (2018) proved the negative effects of ethanol on fetal development [4]. In our study in 2015 [13], which examines the dynamics of ultrastructural changes in the choroid and retina of white rats after intra-abdominal injection of a mixture of alcohols (40% Ethanol and 100% Methanol) in a ratio of 3:1, at different doses of methanol, it was found that after 1 hour and 10 minutes of observation, the initial pathological changes in the endothelial cells of vessels and capillaries of the choroid, in the cells of the pigment epithelium, in the synapses of photoreceptor cells and in the processes of Mueller cells of the retina, which are located below the outer border. In the dynamics of the study, these changes progress and involve in the pathological process of all retinal structures, which last up to 3 months of the study. With increasing doses of methanol in the mixture, the destructive processes in the vascular and retinal membranes become deeper. It should be noted that experimental studies on ultrastructural changes in the LV of rats caused by a mixture of 40% ethanol and 100% methanol, in the available world literature is not found.

*Purpose of work*: to study the dynamics of ultrastructural changes in glial cells and nerve fibers of the optic nerve, which are caused by 40% ethanol solution and 100% methanol in a ratio of 3:1 with a dose of methanol 0.75 g/kg body weight of rats.

## Materials and methods

This work was performed in the framework of the research topic: "Study the effect of a mixture of ethyl and methyl alcohols on the structure of the optic nerve of rats" № state. registration 0120U103694.

The work was performed on 43 adult Wistar rats weighing from 250 g to 300 g, divided into 3 groups: I - experimental group in which the rats were injected intraperitoneally with a mixture of alcohols (40% ethanol solution and 100% methanol) in a ratio of 3:1 (dose of methanol in which is 0.75 g/kg body weight of rats); II - experimental group in which rats were injected intraperitoneally with 100% methanol at a dose of 0.75 g/kg body weight; III - (control group), in which water for injection is injected intraperitoneally in a volume similar to the previous groups.

Animal manipulation and euthanasia were carried out in accordance with the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Purposes (Strasbourg, 1986). Tissues for the study were treated according to the conventional method of electron microscopy. The orbital part of rats ON, which was obtained after enucleation of the eyeball with ON, which were in a state of deep anesthesia, was investigated using an electron microscope PEM-100-01 (Ukraine) 3 hours, 1, 3, 7 and 14 days after administration.

## Results

Electron microscopic examination 3 hours after the introduction of a mixture of alcohols in the structure of optic nerve shows enlightenment of the axoplasm, vacuolation of mitochondria and detachment of the axolemma of individual large caliber NF. Glial cells of ON in this period of the experiment remain virtually unchanged, except for mitochondria, some of which have an enlightened mitochondrial matrix with no or partial destruction of the cristae and expanded individual tanks of the granular endoplasmic reticulum (GER) (Fig. 1, 2).

In the period from 1 to 7 days, alternative changes in ON progress somewhat, especially in the first 3 days. The changes that were characteristic of the previous period were supplemented by stratification of the myelin sheath of almost all NF, edema of the axoplasm and its detachment from the myelin sheath of some NF, pathology of mitochondria and a decrease in the number of structures in the axons. In glial cells, both in the perinuclear part of the cell and in its processes surrounding the NF, the phenomena of hydropic dystrophy are determined (Fig. 3).

On the 14th day of observation, the signs of edema in the studied structures of ON are somewhat reduced, with the exception of large-caliber NF, the ultrastructure of which

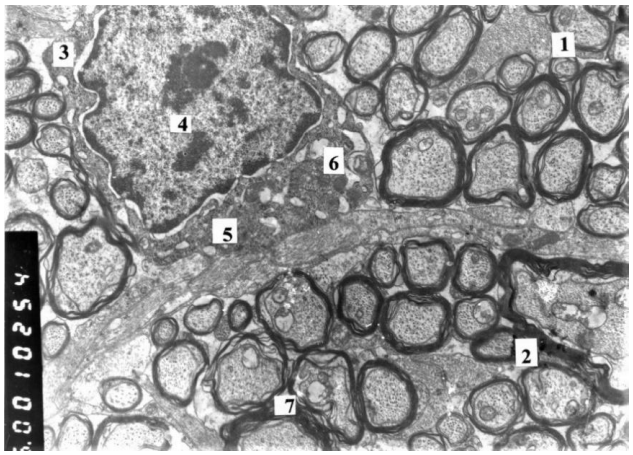


**Fig. 1.** Ultrastructure of the optic nerve of the rat 3 hours after injection of WFI. Nerve fibers and the glial cell are unchanged. Electronic microphotography. x6000. 1 - optic nerve, 2 - nerve fibers, 3 - glial cell, 4 - nucleus, 5 - cytoplasm, 6 - mitochondria, 7 - myelin sheath.

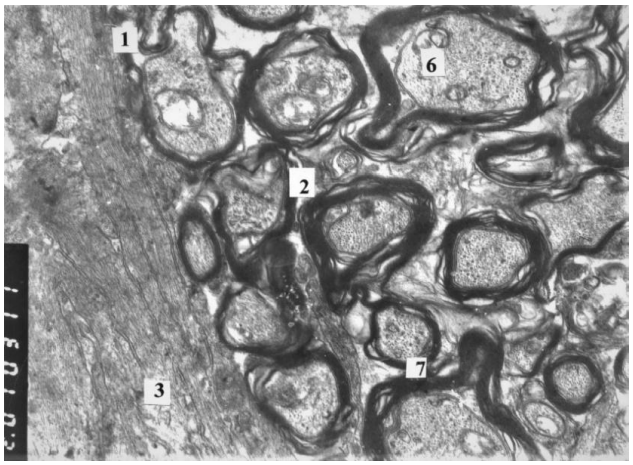


**Fig. 2.** Ultrastructure of the rat optic nerve 3 hours after intra-abdominal injection of a mixture of solution of ethanol 40% and methanol 100%. Destruction of mitochondrial cristae and axolema detachment in axons, deformation and stratification of medullary sheaths in nerve fibers. Electronic microphotography. x12000. 1 - optic nerve, 2 - nerve fibers, 3 - glial cell processes, 6 - mitochondria, 7 - myelin sheath.

practically does not differ from those described in the previous terms. Glial cells are characterized by heterogeneity: some with hydropic dystrophy and degeneration of organelles, some with a structure close to normal or with elements of compensatory-restorative processes, ie with an increase in the number of organelles that perform protein-synthesizing and energy-forming functions.

In ON after injection of 100% methanol from 3 hours to 14 days, the ultrastructure changes are unidirectional in nature with changes in its structures after the II mixture of alcohols. However, pathological changes in them in the period from 3 days to 14 are more extensive and deeper. However, in the initial period, the elements of edema of the structures of the optic nerve, which are found in the material of 1 group of animals, are somewhat smaller. At the same time, the phenomena of compensatory-restorative processes in the structures of ON in this group of rats are more active (Fig. 4).

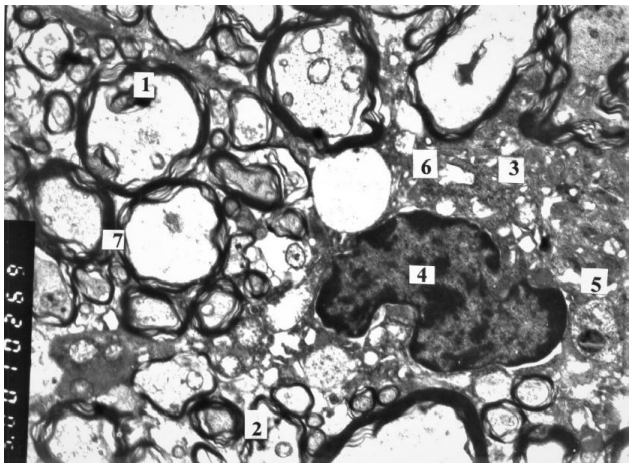


**Fig. 3.** Ultrastructure of the optic nerve of the rat one day after intra-abdominal injection of a mixture of solution of ethanol 40% and methanol 100%. Hydropic changes of membrane organelles in the glial cell. Edema of the axoplasm, vacuolization of mitochondria and stratification of the medullary sheath in nerve fibers. Electronic microphotography. x5000. 1 - optic nerve, 2 - nerve fibers, 3 - glial cell, 4 - nucleus, 5 - cytoplasm, 6 - mitochondria, 7 - myelin sheath.

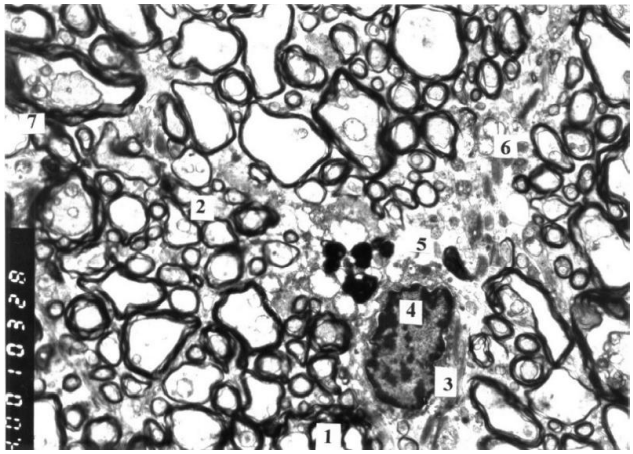


Fig. 4. Ultrastructure of the optic nerve of the rat 14 day after intra-abdominal injection of methanol 100%. Hydropic dystrophy of axons of nerve fibers. Destruction of cytoplasmic structures and damage to glial cell plasmolemma. Electronic microphotography. x4000. 1 - optic nerve, 2 - nerve fibers, 3 - glial cell, 4 - nucleus, 5 - cytoplasm, 6 - mitochondria, 7 - myelin sheath.

## Discussion

Analysis of the material studied by us showed that 3 hours after II mixture of alcohols, with a small dose of methanol, causes changes in the structure of large NF caliber, characterized by axoplasmic edema, stratification and deformation of the myelin sheath, mitochondrial pathology, which probably leads to a decrease their excitability and disrupts the conduction of nerve impulses,

as well as hydropic changes in the membrane organelles of individual glial cells, especially mitochondria, which inhibits the supply and recovery of NF. The same type of changes was also found in patients after poisoning by low-quality alcoholic beverages, which is confirmed by a number of authors [7, 18]. In addition, more significant hydropic changes in the structures of ON in 1 group after 3 hours of study than in the material of group 2, most likely found due to faster permeability ethanol through the membranes of cells, as evidenced by N.Ya.Golovenko and co-authors (2008). By day 7 of observation, alternative changes in the ultrastructure of ON increase and are manifested by the phenomena of hydropic dystrophy and degeneration, also involving small and medium-sized NF and most glial cells, some of which are in a state of necrosis. However, the detected changes in the structures of ON are somewhat reduced to 14 days of observation and mainly in NF of small and medium calibers and part of glial cells. From the 1st day of observation in axons and glial cells, reparative processes also appear in parallel, but they are much slower. In this regard, as clinical studies show [12, 27], the recovery of visual acuity in victims after methanol poisoning is very slow.

In ON after injection of 100% methanol, the pathological changes are unidirectional, but more extensive. On the 14th day, the signs of edema in the structures of ON, as in the animals of the previous group, are somewhat reduced, but their pathological manifestations in this group of animals are more significant, especially among glial cells. At the same time in the cells of this group of animals are more active protein-synthesizing and energy-producing processes, there are also binuclear glial cells, which, in general, enhances trophic and recovery of NF, but despite this in the studied structures are still stable and profound destructive changes. This may be due to the fact that methanol slowly penetrates into cells, but is also slowly released from them, forming toxic metabolites [9, 10, 15].

It should be noted that mitochondria are the most vulnerable organelle due to the action of alcohols, in particular methanol, both in glial cells and in the axons of NF in all periods of observation. As a result, the main function of mitochondria changes - the production of energy so necessary for cells to function normally, that is, - suffers oxidative phosphorylation, which affects cell viability and leads to pathology.

It can be assumed that methanol primarily affects the mitochondria, or perhaps a significant amount of energy is expended to restore the ultrastructure and function of the optic nerve due to the destructive effects of methanol. E.Icel and co-authors (2020) in their work also point to the pathology of mitochondria in the optic nerve after methanol poisoning [7]. Other sources contain information on the pathology of mitochondria in the nervous system under stress of various natures [3, 5]. At the same time, as shown by the author E.Icel and co-authors (2020), intravenous administration of ATP had a significant positive effect on the parameters of oxidative stress and the structure of the optic nerve in rats poisoned with methanol [7]. B.Setiohadji and co-authors (2018) also suggest the use of antioxidant therapy as a possible treatment for toxic optic neuropathy caused by methanol.

Thus, we have shown that, despite a small dose of methanol in a mixture of alcohols, in the elements of the optic nerve there are pathological changes similar to those observed after the use of 100% methanol in a similar dose. We confirmed that ethanol in the applied proportion with methanol in a mixture of alcohols slightly reduces pathological manifestations in the optic nerve at the initial stages of observation, but in the dynamics of the study found that the leading place in the development of pathological changes is methanol. R.A.Rasheed and co-authors in their work published in 2017 also proved the protective effect of ethanol on the retina of rats in acute methanol poisoning [16].

The data obtained by us make it possible to judge some aspects of the toxic effects of both a mixture of alcohols and 100% methanol on the ultrastructure of the optic nerve and to determine the initial pathological changes caused by these substances.

## Conclusions

1. It was found that a mixture of 40% ethanol solution with 100% methanol and 100% methanol (at a dose of 0.75 g/kg body weight of rats), after 3 hours of observation cause axoplasmic edema, myelin sheath stratification and nerve mitochondrial pathology large-caliber fibers with reactive changes in glial cells. After injection of the alcohol mixture, these changes are less pronounced.

2. In the dynamics of the study (up to 14 days) in glial cells and axons of nerve fibers there are phenomena of hydropic dystrophy with alteration of organelles, stratification and deformation of myelin sheaths of nerve fibers.

3. The established changes are most pronounced on the 3rd day after injection of a mixture of alcohols and on the 7th day of observation after the use of 100% methanol, but in the initial period after intra-abdominal injection of a mixture of alcohols they are less pronounced. At all times of observation in the studied structures of both experimental groups of animals revealed pathological changes in mitochondria.

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**ДИНАМІКА УЛЬТРАСТРУКТУРНИХ ЗМІН В ГЛІАЛЬНИХ КЛІТИНАХ ТА НЕРВОВИХ ВОЛОКНАХ ЗОРОВОГО НЕРВУ ЩУРІВ, ВИКЛИКАНИХ ВНУТРІШНЬООЧЕРЕВНИМ ВВЕДЕННЯМ СУМІШІ 40% РОЗЧИНУ ЕТАНОЛУ І 100% МЕТАНОЛУ**

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*Доволі часто зустрічаються випадки отруєння населення неякісними алкогольними напоями, до складу котрих входить метанол. У постраждалих первинно вражається зоровий нерв, сітківка і тканини головного мозку. Проведено багаторічне дослідження, направлене на виявлення початкових структурних змін у зоровому аналізаторі при застосуванні різних доз метанолу та його суміші з етанолом. Мета роботи: вивчити динаміку ультраструктурних змін у гліальних клітинах та нервових волокнах зорового нерву, які викликані 40% розчином етанолу і 100% метанолом у співвідношенні 3:1 з дозою метанолу 0,75 г/кг маси тіла щура. Дослідили ультраструктуру очноямкової частини зорового нерву 43 дорослих щурів лінії Вістар у період від 3 годин до 14 діб після одноразової внутрішньочеревної ін'єкції суміші 40% етанолу і 100% метанолу та 100% метанолу, доза метанолу становить 0,75 г/кг маси тіла щура. У щурів ЛД50 складає 9,5 г/кг маси їх тіла. Виявлено, що через 3 години після ін'єкції суміші спиртів розшаровувалась мієлінова оболонка нервових волокон великого калібру, набрякала аксоплазма та патологічно змінювались мітохондрії в їх аксонах, відбувалась альтерація мітохондрій в гліальних клітинах, що впливало на якість проведення нервових імпульсів та аксоплазматичний транспорт речовин. У динаміці дослідження альтеративні зміни в структурах зорового нерву прогресували з повним руйнуванням частини гліальних клітин до 7 доби, переважно в перші 3 доби. Після застосування 100% метанолу зміни в структурах зорового нерву були аналогічними змінам в них після застосування суміші спиртів, але з більш значною патологією у всі строки спостереження з піком їх прояву на 7 добу. В гліальних клітинах і в аксонах нервових волокон з 1 доби дослідження виявлені ознаки компенсаційно-відновних процесів: у них посилювались білок-синтезуюча та енергоутворююча функції, які були направлені на відновлення пошкодженої ультраструктури. Встановлено, що через 3 години після ін'єкції суміш спиртів відбуваються реактивні зміни в структурах зорового нерву щурів, які з 1 доби переростають в патологічні зміни і спостерігаються до 14 доби з піком їх активності на 7 добу дослідження. Після застосування 100% метанолу ультраструктура зорового нерву щурів більш пошкоджена, ніж після ін'єкції суміші спиртів. Доведено, що провідне місце в розвитку патологічних змін в структурах зорового нерву після ін'єкції суміші спиртів відводиться метанолу.*

**Ключові слова:** *ультраструктура, гліальні клітини, нервові волокна, зоровий нерв, суміш спиртів, етанол, метанол.*