



REVIEW PAPER

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The effect of alcohol on neuroglia in the developing brain and in adults

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Abstract

Introduction. During puberty, the young body undergoes transformation not only within the reproductive and hormonal systems, but also significant changes in the central nervous system (CNS). Matured neural connections improve the integration of distant brain regions, the plasticity of neurons increases, and thus specialization of the brain occurs in the performance of specific tasks. During these transformations, both neurons and the accompanying neuroglia are sensitive to all toxic factors, among which ethanol occupies a special place. It causes an increase in the activity of glial cells, which by directing pro-inflammatory cytokines directly contribute to the death of apoptotic neurons. A long-lasting and irreversible impairment of brain function, especially in the hippocampus occurs as a result of alcohol abuse during the period of development.

Aim. This paper presents an overview of current knowledge about the effects of alcohol on neuroglia in the developing brain and in adults.

Materials and methods. The literature review of the following databases has been conducted: EBSCO, PubMed, Science Direct, Springer Link.

Conclusions. The results of alcohol research have shown that it affects the neurotransmission and fluidity of cell membranes, changing the activity of neurons. By binding to GABA receptor (GABA) and N-methyl-D-aspartate receptors (NMDA receptor for glutamate), ethanol suppresses brain function. In addition to increased sensitivity and susceptibility to the addictive effects of ethanol, the neurogeneration activity is intensified followed by the induction and release of pro-inflammatory cytokines, which in the first stage disrupt the cortical function hindering logical thinking and disrupting the limbic system, directly affecting the memory and learning processes. Next, the cerebellum is attacked, which results in the impairment of balance and motor coordination, and consequently acts on the brain stem, directly affecting the respiratory and circulatory control centers.

Keywords. brain, alcohol, neuroglia

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Introduction

For a long time it was believed that glial cells are mainly supportive, nutritious and adjuvant to neurons. In the era of the science progress and the development of histological techniques, the knowledge about neurocognitive cells has been extended to include their active participation in the neuronal functions of information transfer and neuronal plasticity, which forms the basis in the processes of learning and memory. Glial cells alone do not conduct nerve impulses, but supports neurons in this function. Neuroglia has important functions in forming synaptic structures, and thus in synaptic transmission, and participates in developmental myelination of nerve fibers.¹ The results of alcohol research showed not only increased susceptibility of the brain to the addictive effects of ethanol, but also increased activity of glial cells that contribute to the release of factors associated with inflammation. The consequence of this process are morphological changes in myelin sheaths leading to the death of apoptotic neurons. In addition, these processes are accompanied by impairment of cognitive abilities and disturbances in behavioral responses. Interactions between glial cells suggest that therapies of alcoholism based on the pathology of specific types of neuroglia may contribute to the understanding of interactions between different brain cells.²

Alcoholism

According to the definition of the National Institute of Alcohol Abuse, alcoholism is a chronic, recurrent cerebral disease, consisting of compulsive use of alcohol, loss of control over its consumption and a negative emotional state in the absence of it. The consequences of alcohol abuse are various pathologies e.g. behavioral or neurological ones, which are dependent on metabolic disorders at the cellular level. Such disorders in the nervous system contribute to the incorrect exchange of information between brain centers that control alcohol consumption and regions involved in emotional and cognitive regulation. This leads to significant changes in the structure and functioning of the brain, and neuropathological consequences lead to dementia. Alcohol-induced brain changes are also reflected in structural damage in the gray and white matter.³

Glial cells

CNS disorders are more and more often considered not only related to neuronal dysfunction, but to a large extent controlled by inflammatory processes controlled by glial cells. In many neurodegenerative diseases, e.g. in multiple sclerosis (MS), Alzheimer's disease (AD), stroke or Parkinson's disease (PD), glial cells are involved in the disease process.^{4,5} The normal activity of neurons and their survival are fully dependent on interaction with glial cells that support them in neurotrans-

mission, strengthen functional potentials, participate in the repair of brain damage, act neuroprotective and are involved in providing substrates necessary for the production of many neurotransmitters, as well as in their decomposition. Ependymal glia, astrocytes, oligodendrocytes are the basic cells present in CNS apart from the neurons.¹ Microglia and astrocytes are responsible for the immunological functions and play a key role in the inflammatory response. It is presumed that astrocytes can be formed indirectly from radial glia, one of which is the formation of scaffolding for newly formed neurons.⁵

One of the astrocyte divisions relates to their ability to respond to CNS damage. Inactive, resting and reactive astrocytes were distinguished. The resting type exists in normal, unchanged glial tissue in the CNS, while reactive astrocytes locate closer to the site of injury and together with microglia participate in the formation of glial scars.⁶ Astrocytes support a number of activities necessary for the functioning of neurons, including participation in the formation and maintenance of selective, necessary for the proper functioning of the CNS blood-brain barrier (BBB) thus protecting the brain from the influx of toxic substances and ions, regulate extracellular concentrations of ions and neurotransmitters, synthesize metabolic substrates for neurons (glycogen, sterols and lipoproteins), remove excess neurotransmitters (glutamate) released by active neurons.⁷ In addition, they secrete growth substances such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) or fibroblast growth factor (FGF) playing important roles in the repair and growth processes of neurons. Like most glial cells, astrocytes may play a primary role in CNS diseases⁸. Microglia ensures maintenance of homeostasis in the CNS, monitors the survival of neurons and acts as immunologically competent cells. The microglial cells originate from macrophages located outside the nervous system and are dispersed throughout the CNS. They migrate to the nervous system during fetal life. In the normal brain and spinal cord, microglia cells are inactive, which is why they are called rest microglia. When damage occurs in the CNS, the number of these cells increases rapidly and become effector cells of the immune system. Activation of microglia results in a change in their morphological characteristics. Their proliferation, changes in receptor expression and change in function are induced, and the stimulus that contributes to such changes is most likely the depolarization of the neuronal membrane that arises as a result of damage. A significant part of activation of microglia also play pro-inflammatory cytokines, growth factors, complement proteins, free radicals, neurotoxins, nitric oxide, prostaglandins, ATP and stimulating amino acids. Activated microglial cells are able to produce many growth and inflammatory factors.⁹⁻¹³

Ependymal glia plays key roles in the processes of CNS development and physiology. Under normal conditions, specialized ciliated ependymal cells create a cerebrospinal fluid barrier - the brain, participating actively in cellular filtration in CNS.¹⁴

The speed and efficiency of nerve impulses transmission within the nervous system is based on the presence of myelin sheaths - structures produced by oligodendrocytes, which protrusions form a spiral membrane around the axons of many neurons. Oligodendrocytes appear and differentiate last in the developing brain. They actively participate in the metabolic transformation of neurons due to the possibility of supplying them with iron.¹⁵ Oligodendrocytes are mainly associated with the white matter of the brain, and their main functions include the formation of myelin sheaths around neuronal scars. Damage to white matter and loss of oligodendrocytes are features of many neurodegenerative diseases. In response to oligodendrocyte damage, oligodendrocyte precursor cells (OPCs) initiate their proliferation and differentiation for remyelination. During the destruction of oligodendrocytes, their cytoplasm vacuoles and their nucleus becomes pyknotic. Although the mechanisms of oligodendrogenesis and remyelination in CNS diseases are still largely unknown and under-researched, support for other glial cells and neurons is necessary for the proliferation and differentiation of OPC.¹⁶⁻¹⁸ Understanding these complex glial-neuronal interactions may contribute to the treatment of brain injuries and neurodegenerative diseases.^{1,19}

Effect of alcohol on glia and central nervous system (CNS) structures

Post-mortem examinations in humans have shown that long-term alcohol intake leads to myelin damage to various degrees, causing its damage at the macroscopic level. Disorders of myelin sheaths have been observed in diseases such as Marchiafavi-Bignami's disease, Wernicke-Korsakoff syndrome, hepatic encephalopathy, central pontine myelinolysis, alcoholic cerebellar degeneration, and these mainly affect the areas of the white matter of the brain. In these disorders, BBB damage occurs or nutritional deficiencies associated with lack of thiamine occur.²⁰

One of the areas most exposed to ethanol is the corpus callosum (CC), which is the place where information is transmitted between the right and left hemispheres of the brain. Human CC begins to develop around the fifth week after fertilization, at the time of formation of brain follicles and continues throughout the second trimester. During this period of life, the developing brain is the most sensitive to alcohol. This area of the white matter consists mainly of about 200 million myelinated axons, which carry nerve impulses to the receptors, glial cells - mainly oligodendrocytes and blood vessels.²¹ CC is an in-

tegral part of motor function and is involved in higher cognitive processes such as verbal learning, memory, processing of abstract or complex concepts.²²

In studies relating to the CC area in alcoholism, it has been shown that there is a significant reduction of oligodendrocytes and a decrease in the expression of genes associated with specific myelin proteins such as: myelin basic protein (MBP), myelin proteolipid protein (PLP), myelin-associated glycoprotein (MAG) or 2'3'-cyclic nucleotide 3' phosphodiesterase (CNP) that are necessary for its production.²³ In the case of CC the strongest atrophy is observed in its parts: trunk (body), genu and splenium. This applies mainly to damage to sheaths and blood vessels.²⁴ Alcohol disturbs the expression of major oligodendrocyte and myelin proteins, and during prenatal development it can induce oligodendrocyte apoptosis, leading to drastic reduction of already differentiated oligodendrocytes and their progenitor cells in the CC area. After discontinuation of exposure to alcohol, the populations of these cells return to the original number. However, it has been shown that in young adult mice there are shortages in the level of MBP or in the structure of nerve fibers in the CC area.^{25,26}

The CC atrophy in alcoholics is correlated with the consumption of alcohol throughout all life. It is particularly evident in the prefrontal area of CC in patients with Wernicke's alcohol encephalopathy, and the extreme manifestation of alcohol toxicity in CC is Marchiafava-Bignami disease, which mainly affects older alcoholics. It is characterized by demyelination, necrosis and cystic degeneration of the middle layer of CC.²⁴

Other areas of the brain exposed to the harmful effects of alcohol are the forebrain and the cerebral cortex, which are the first to manifest disorders related to motor coordination and disturbances in the thinking process. The effect of these changes is the loss of control over emotions, increased memory loss for which the midbrain is responsible, and as a consequence, the most important vital activity centers located in the brain stem are damaged.²⁷⁻²⁹

Animal studies show that high doses of alcohol inhibit the growth of new neurons, and this deficiency causes long-term deficits in key areas of the brain such as the hippocampus.^{30,31} Even a small dose of alcohol, especially during adolescence, contributes directly to the reduction of its volume and difficulties in acquiring knowledge. Until recently, it was assumed that the number of neurons in the adult brain was established early in life, but it turned out that new cells are generated in adults by neurogenesis. They originate from stem cells that can divide without limitations, renew and initiate the growth of different cell types. Discovery of brain-stem cells and neurogenesis in adults allowed a new way to look at the problem of alcoholic changes in the brain.³²

Drinking alcohol during pregnancy can cause many changes in the brain of the developing fetus, which are associated with both physical and mental development. The most known and the most serious syndrome of congenital malformations in children is a group of conditions, called fetal alcohol syndrome (FAS). Children with FAS have different facial features and are significantly smaller than average. Their brains contain fewer nerve ganglia and fewer neurons able to function properly.^{33,34} Incorrect activation of the developing immune system can have long-term negative consequences. There is an increase in the level of such pro-inflammatory cytokines as: IL-1 β , TNF- α , CD11b, CCL4 and TGF- β , which activates microglial cells especially in the hippocampus. Activation of microglia contributes to deficits in learning and memory, especially in children diagnosed with FAS. The effect of these activities is the induction of neuroimmune responses, resulting in long-term changes in cognitive functions and behavior.³⁵

Particular sensitivity to harmful effects of alcohol during adolescence was observed in the olfactory and peri-nasal cerebral cortex areas of rats. In these areas there are time intervals known as “windows” with a decidedly high and selective susceptibility to the harmful effects of alcohol. Ethanol induces sensitization and potentiation of neuronal conduction along with intense prefrontal cortex activation, predisposing to increased alcohol intake and addiction in adult life.³⁶

Glial cells are actively involved in the immune response in the CNS, and their dysregulation has a significant impact on brain damage leading to neurodegeneration. Glial cells play a significant role in the CNS immune response. Ethanol has immunomodulatory activity and induces specific changes in tissues and organs. These effects depend mainly on the type of cells and the dose of ethanol. Even low ethanol concentrations stimulate inflammatory processes in the brain and glial cells by increasing the expression of cytokines and inflammatory mediators and by activating signaling pathways involving kinases and inflammatory transcription factors. Receptors that recognize the so-called Molecular patterns associated with pathogens that include Toll-like receptors (TLRs) such as TLR4 / IL-1RI can be involved in ethanol-mediated inflammation because they activate specific signaling pathways inside the cells and by blocking them eliminate the production of alcohol-induced status mediators inflammatory and cell death.² Chronic alcohol exposure induces atrophic features in astrocytes, mainly in the hippocampus, causing a reduction in their number in the general glial cell population. The reaction of astrocytes to pathogenic alcohol exposure is not limited only to changes in their number, morphology or development, but disrupts the regulation of neuro-inflammatory processes, calcium signaling and inhibits the neurotransmission and water-electrolyte balance.

As a result of the action of alcohol, there is a simultaneous change in the number of astrocytes and a decrease in the number of their markers, mainly glial fibrillary acid protein (GFAP), which may be the direct cause of degeneration of neurons.³

The harmful effect of alcohol contributes to the damage of glial cells, disrupting the activity of neurons. Neuronal signals, which directly translate into the physiology of glial cells under the influence of alcohol, significantly interfere with the development, morphology, physiology and gene expression of astrocytes, oligodendrocytes, and microglia. The effects of alcohol on oligodendrocytes were among the first to draw the attention of clinicians because they caused serious neurological and cognitive disorders in connection with myelin pathology.^{3,37}

Long-term alcohol abuse usually leads to loss of the white matter of the brain and impairment of the executive function. In addition to chronic degenerative neuropathology, alcoholics are predisposed to the development of potentially life-threatening brain stem damage due to a deficiency of thiamine, which has no toxic effect on neuroglia, myelin sheaths and microcirculation.³⁸

The process of myelination of cortical neurons increases during puberty, increasing the speed and efficiency of nerve conductivity, improving communication between different areas of the brain, leading to rapid neurological and neurochemical changes. New connections between neurons which is closely correlated with pulse control, memory, speech and movement are created. During embryonic development, mainly glial cells are exposed to teratogenic effects of ethanol.^{39,40}

Destructive, apoptotic effects of alcohol on oligodendrocytes, especially in the areas of CNS white matter and neurons in the developing brain, may explain the wide range of neuropsychiatric disorders as a consequence of even short-term exposure to alcohol during fetal life. Destroying oligodendrocytes that begin to myelinate axons can lead to long-term and irreversible neurobehavioral disorders. Sensitivity of neurons to apoptosis is associated with the period of rapid synaptogenesis, while oligodendrocytes coincide during the most intense myelination.³² Oligodendrocytes have been shown to undergo maturation changes in the third trimester of pregnancy in the macaque. The emerging oligodendrocyte precursor cells first differentiate into promyelinating cells and then into the myelinating oligodendrocyte.³⁹

It is not known whether the alcohol inducing oligodendrocyte apoptosis is dependent on the same mechanism (blockade of NMDA glutamate receptors and hyperactivation of GABA receptors), which causes neuroapoptosis. Existing signaling between neurons and oligodendrocytes via synapses, suggests similar mechanisms of cell surface receptors triggering these two toxic phenomena. The specificity of alcohol-induced apopto-

sis lies in the fact that the cell death of both neurons and oligodendrocytes is mutually symmetrical. The death of brain cells exposed to alcohol is accurately reflected by the same number and distribution of dying cells among homologous populations of cells in the opposite hemisphere. This feature of alcohol neurotoxicity can significantly reduce the ability to recover function, because the extent of recovery can depend on the availability of intact opposite populations of cells with similar functional properties.³⁹

In addition to the impairment of myelination, even short-term exposure to alcohol disturbs the processes of gliogenesis, weakens immune function and the time of inflammatory reactions, leading to increased susceptibility to infection. The consequence of these changes is the atrophy of the brain in adults and the reduction of glial cells mainly in the hippocampus.³ Through the direct influence of alcohol on neuroglia, specific neurocognitive proteins are damaged, which contributes to the formation of oxidative stress and loss of metabolic support for neurons, which also interferes with neurogenesis.^{41,42}

Due to the key roles of astrocytes and oligodendrocytes in neurotransmission and signal transduction, these cells most likely play a central role in the molecular mechanisms underlying communication disorders associated with alcoholism between different areas of the brain. It has been shown that there are markers of astrocytes that change in response to ethanol exposure or during its discontinuation. These include intercellular protein, glutamate transporters, and enzymes associated with glutamate and GABA metabolism. Both changes in proteins and their regulatory pathways cause dysfunction of gray and white neurons in the CNS. In addition, alcohol alters the expression of astrocytes and myelin proteins as well as oligodendrocyte transcription factors relevant to the maintenance and plasticity of myelin sheaths. These changes accompany DNA and histone modifications resulting in abnormal gene expression and protein translation.³

It has also been shown that alcohol may cause permanent changes in the regulation of cytokines and the sensitivity of the hypothalamic-pituitary-adrenal axis, resulting in an immunosuppressive effect, which may increase susceptibility to infection.⁴³⁻⁴⁵

In conclusion, alcohol is a well-known cytotoxic agent that causes various types of damage in the brain. Even short-term brain exposure to alcohol during puberty shows a long-term impairment of the brain function that does not disappear with age. Changes in the adolescent brain are difficult to detect because they have a significant impact on long-term thinking and memory processes. Understanding the mechanisms of alcohol influence on long-term memory and the ability to learn people who abuse alcohol, will allow the appropriate prevention of alcohol addiction treatment.

Conclusions

- Alcohol consumption causes structural and functional changes in the brain cells.
- Changes in the brain caused by alcohol are irreversible.
- Exposure to ethanol during puberty has a significant impact on the limbic system responsible for memory and learning processes, causing cognitive deficits and behavioral disorders during adulthood.
- During the development and puberty period, alcohol can cause irreversible changes that affect a person's life.

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