INTERNATIONAL JOURNAL OF INTEGRATIVE AND MODERN MEDICINE

Alcoholism as a Factor in the Development and Spread of Diseases

Khusenov O. N.
Bukhara Medical Institute

Abstract: Within the framework of this review, modern medical views on the nature of alcoholism and its impact on the development and spread of various diseases are presented. It also characterizes the pathogenesis of alcoholism at the molecular level, provides data on disorders of carbohydrate metabolism, immune system, cell death, modulation of mitochondrial permeability and modulation of gene expression due to the influence of alcohol. progression of infectious diseases (tuberculosis, pneumonia), cancer, diabetes, diseases of the nervous system (alcoholic polyneuropathy, Wernicke's encephalopathy), cardiovascular diseases (hypertension, coronary heart disease), liver diseases (hepatitis, cirrhosis), as well as pancreatic diseases (pancreatitis). A special place in the review is occupied by the description of the role of alcohol in the spread of sexually transmitted infections (STIs): syphilis, chlamydia, ureaplasmosis, gonorrhea, HIV infection, herpes simplex, trichomoniasis. In this case, the influence of several factors was recorded. The first is associated with changes that occur in the body as a result of excessive alcohol consumption - in particular, with a weakened immune system and/or a decrease in the effectiveness of treatment. Another factor is related to promiscuous antisocial behavior, often inherent in persons suffering from alcohol dependence.

Keywords: alcoholism; sexually transmitted infections, infectious diseases.

Alcoholism is a preventive illness that is determined by a pathological influence to the physical, psychic and physical dependence, the development of a dispositive state of alcohol consumption, and in the case of the above-mentioned by the so-called co-operative relations and psychological degration.

In the last decade, the scale of research on genetic predisposition to alcohol pathology has been increasing, which indicates that polymorphic variants of genes of neurotransmitter systems, enzymes of ethanol metabolism play a role in the formation of alcoholism;

Neural networks involved in synaptic transmission are highly regulated by ethanol in people with chronic alcohol dependence [16].

Exposure to ethanol causes profound changes in the reward system of the brain, which leads to noticeable disturbances in the mechanisms of the motivational state. The meso-limbic dopamine system is part of the motivational system that regulates appropriate behavioral responses to natural reinforcements, such as food, drink, and beverage. Natural rewards rarely cause long-term changes in the mesolimbic system; Nevertheless, alcohol, like all other drugs, acutely activates it and, with chronic exposure, produces long-term functional disorders. Constant functional reorganization of the reward system leads to a change in homeostasis relative to a new setting point, such a change is called allostasis. These long-term neuroadaptations contribute to the development of cravings and relapse [10]. In addition to the influence of neurochemical processes, hormonal cycles have a strong influence on the course of this disease [2, 20].

Stages of pathogenesis of alcoholism. The course of alcoholism up to the formation *of alcohol withdrawal syndrome* (ALS) has three stages, sharply differing in progression: before the onset of abuse (on average 5 years), from the beginning of abuse to the appearance of craving for alcohol / change in the nature of intoxication (1-2 years) and further to the appearance of AAS/amnesia (1-2 years). The later systematic use begins, the longer the time before the onset of AAS [2].

Ethanol is metabolized in the body by *alcohol dehydrogenase* (ADH) and *aldehyde dehydrogenase* (ALDH); both enzymes have several forms encoded by different genes. To date, the most studied coding variants are ADH1B, ADH1C, and ALDH2; some ADH1B and ADH1C alleles encode

particularly active enzymes, resulting in faster alcohol conversion [3] The distribution of *ADH1B* and *ALDH2* variants varies widely among different populations; protective alleles are most common in people in East Asia, however, changes in genes encoding ADH enzymes affect the risk of alcoholism in other populations; e.g., *ADH4* are found in populations of European origin [6].

More than 90% of ethyl alcohol that enters the body is completely oxidized to acetic acid. This process occurs mainly in the liver. The rest of the alcohol is not metabolized and is excreted in the form of sweat, urine, or excreted during respiration [1].

Alcohol abuse leads to disorders of carbohydrate metabolism, cell death, modulation of mitochondrial permeability, and modulation of gene expression [4].

Carbohydrate metabolism disorder: NAD^+ is an intermediary of cytosolic energy metabolism, affects glycolysis, the conversion of lactate to pyruvate by *lactate dehydrogenase* (LDH). Depletion also causes inhibition at later stages of glucose metabolism – a decrease in the oxidation of acetyl-CoA in the Kreps cycle; the accumulation of NADH inhibits pyruvate dehydrogenase, reducing the conversion of pyruvate to acetyl-CoA, which contributes to the enhancement of conversion of pyruvic acid to lactate in the cytosol of cells.

Cell death: Mitochondria secrete pro-apoptosis factors such as cytochrome C and apoptosis-inducing factor, which activate caspase-dependent and caspase-independent cell death pathways, respectively. Another important activator of caspase-independent cell death is the enzyme NAD^+ ADP-ribosyltransferase 1(PARP-1), a mediator of programmed oxidative stress-activated necrosis. The NADH/NAD^+ ratio also affects mitochondrial permeability, which promotes the translocation of the apoptosis-inducing factor from the mitochondria to the nucleus and ultimately leads to apoptosis [17].

Modulation of mitochondrial permeability: Defined as an increase in the carrying capacity of mitochondrial membranes for molecules of a certain size, this can lead to mitochondrial swelling and cell death by apoptosis or necrosis. An increase in the NADH/NAD^+ ratio as a result of ethanol metabolism results in an increase in channel opening, which significantly affects the mitochondrial membrane potential. increased calcium ion output and inhibition of ryanodine receptors in the heart muscle [13].

Ethanol alters gene expression patterns as a result of the binding of metabolites to transcription factors or modification of chromatin structure. For example, the activity of enzymes involved in epigenetic modifications of DNA, such as histone methylation and acetylation enzymes, is influenced by the levels of the metabolites nicotinamide *adenine dinucleotide* (NAD), *adenosine triphosphate* (ATP), and *S-adenosylmethionine* (SAM); chronic alcohol consumption leads to a significant decrease in SAM levels, thereby contributing to DNA hypomethylation [14].

The role of alcohol in the formation and progression of diseases of various body systems. Diseases for which alcohol is one of the causes (listed in the order of their ICD-10 codes):

Infectious diseases, cancer, diabetes, diseases of the nervous system, cardiovascular diseases, liver and pancreas diseases.

One of the ways to increase the risk of infectious diseases such as tuberculosis, HIV, pneumonia is to suppress the immune system, especially with chronic consumption of large doses of alcoholic beverages; On the other hand, the development of infections is facilitated by unfavorable social living conditions in which people suffering from alcoholism can be [9, 21].

A causal relationship between alcohol consumption and cancer of the mucous membrane of the digestive, respiratory tracts, as well as the liver and mammary glands is confirmed. For those parts of the body where the role of alcohol in the development of tumors has been established, the dose-dependent nature of reactions is determined: the relative risk of carcinogenesis increases in direct proportion to the increase in the volume of consumption of alcohol-containing beverages. The molecular and biochemical mechanisms by which chronic alcohol consumption leads to the development of cancers in various organs are not fully understood; it has been suggested that these

mechanisms involve variations in genes encoding enzymes responsible for ethanol metabolism (e.g., ADH, ALDH, and cytochrome). In addition, according to the International Agency for Research on Cancer, acetaldehyde, which can enter the body either independently or as a product of ethanol degradation, is a strong carcinogen; This can be important in the development of tumors of the digestive tract, especially in its upper parts [11]. Microsomal oxidation, of which P4502E1 is a key component, also plays a role in carcinogenesis processes, especially after chronic excessive drinking; during such metabolism, reactive oxygen species are formed, which bind to DNA and contribute to the formation of altered products with tumorgenic properties. In addition, P4502E1 activates various procarcinogenic compounds that can be converted into carcinogenic compounds in the body [19].

Damage to the nervous system in alcoholism is most often manifested *by alcoholic polyneuropathy* (APN) and Wernicke-Korsakoff syndrome. Wernicke's encephalopathy is an acute neuropsychiatric condition, which is caused at the initial stages by biochemical disorders in the brain tissue as a result of depletion of intracellular thiamine. APN occurs in 10-30% of patients suffering from alcoholism. polyneuropathy, is also thiamine deficiency and the direct toxic effects of alcohol; Thiamine deficiency in alcoholism occurs due to an imbalance in nutrition, impaired absorption of substances due to pancreatitis, or as a result of toxic damage to the intestinal mucosa [7].

A particularly pronounced effect is observed with the effect of alcohol intoxication on the cardiovascular system. For example, the effect of alcohol consumption on the development of hypertension has a direct dose-dependent effect, while the same for both men and women. A similar dose-response relationship exists between alcohol consumption and atrial fibrillation. On the other hand, for cardiovascular disease caused by reduced blood supply to the heart (i.e., coronary artery disease), the association with alcohol consumption is represented by a J-shaped curve, with intermittent protective effects. Alcoholism has a similar effect on the development of ischemic strokes [5].

Alcohol consumption has specific effects on the liver and pancreas, as evidenced by the existence of categories of diseases such as alcoholic liver disease, alcoholic cirrhosis, alcohol-induced acute or chronic pancreatitis [7].

One of the most common causes of morbidity and mortality in patients with alcoholism are infections that occur as a result of impaired immune system function due to the immunomodulatory effect of ethanol. Epigenomic modulation plays an important role in immune system dysfunction, for example, alcohol-induced epigenomic variations alter the developmental pathways of several types of immune cells (granulocytes, macrophages, and T-lymphocytes) and, through these and other mechanisms, contribute to increased inflammatory responses [5].

The first line of immune defense is the mucous membranes of the gastrointestinal tract and respiratory tract; Alcohol consumption causes damage to the tight junctions between the intestinal endotheliocytes, resulting in increased permeability to bacterial molecules. Molecules, for example, of lipopolysaccharides enter the liver through the circulatory system and activate macrophages, stellate cells, damage hapatocytes; Chronic inflammation is formed, aggravating organ damage. In the lungs, alcohol disrupts the integrity of the barrier, reduces the production of chemokines and cytokines in response to infection. Chronic alcoholism has a depressing effect on the production of GM-CSF in epithelial cells [18].

In the study of the effect on volunteers who do not suffer from addiction, the following changes in cellular immunity were revealed: a decrease in the content of CD3+ T- in the peripheral blood

lymphocytes, CD4+ cells, an increase in the number of CD8+ lymphocytes, an increase in NK cells; the number of phagocytic cells also increases, but their ability to absorb microorganisms weakens; At the same time, the programmed death of cells of the immune system (apoptosis) increases. Long-term abstinence from alcohol in patients with chronic dependence leads to the restoration of the functional capacity of immune cells [15].

The role of alcoholism in the spread of *sexually transmitted infections* (STIs). The main STIs include:

syphilis, chlamydia, ureaplasmosis, gonorrhea, HIV, herpes simplex, trichomoniasis. A large number of studies show a connection between alcohol, promiscuous sexual behavior and the associated spread of STIs [12]. First of all, we are talking about chlamydia and HIV infection. According to statistics, an increase in taxes on alcohol products helps to reduce chlamydial infections by an average of more than 10%, which may be a consequence of a decrease in risky sexual behavior. A large number of surveys prove a tendency to develop chlamydia in sexually active people aged 15-25 who have more than three partners and are prone to taking psychoactive substances, including alcoholic beverages [2].

Alcohol intoxication has a negative impact on the progression of HIV infection through several mechanisms, including changes in viral replication, host immunity, and treatment efficacy, as well as behavioral aspects of those infected [13].

Due to sexual promiscuity under the influence of alcohol, there is an increase in the number of co-infections that create an entry portal for the virus, by destroying the mucous membrane of the genital tract or skin, and also cause inflammatory reactions in the genital tract, increasing the concentration of HIV target cells (e.g., CD4+ T-lymphocytes). By increasing viral replication in HIV-infected patients, alcohol contributes to an increase in the concentration of viral particles in semen and in the vagina, thereby facilitating its transmission; thus, alcoholism is positively correlated with the spread of HIV, even with antiretroviral therapy [12].

When examining blood cells taken from HIV-infected people, it was found that a higher multiplication of the virus occurs after alcohol consumption; In such cells, the ability to produce interleukin-2 is also reduced, as a result of which cytokine activity is impaired. In alcoholism, there is an inhibition of CD8 + T-lymphocytes, and accordingly, an attack on viral cells. Other studies have shown that high levels of IL-6 in the blood are positively correlated with high rates of mortality and HIV-infected people with alcoholism. The immunodeficiency virus binds to two specific molecules on the surface of cells: chemokine co-receptors CCR5 and CXCR4, chronic alcoholism increases the number of CXCR4 cells and leads to an increase in the replication of viral particles [15].

One of the common consequences is neurological damage, which can develop with both alcoholism and HIV infection, so their combination contributes to more detrimental effects on brain function, in particular, accelerated aging. Another neurological disorder is peripheral neuropathy, which is inflammation or degeneration of the nerves outside the brain and spinal cord. It is found in about 30% of HIV-infected patients and in almost 100% of AIDS cases [8].

Literature

1. Boggan B. Alcohol, Chemistry and You Metabolism of Ethyl Alcohol in the Body // General Chemistry Case Studies. 2009. №4. P.30–41.
2. Deogan C., Cnattingius S., Mansdotter A. Risk of self-reported Chlamydia trachomatisinfection by social and lifestyle factors: a study based on survey data from young adults in Stockholm, Sweden // Contracept Reprod Health Care. 2012. Vol.17. № 6. P.458–465.
3. Edenberg H. J. Role of Alcohol Dehydrogenase and Aldehyde Dehydrogenase Variants // Alcohol Metabolism Part II: A Key to Unlocking Alcohol's Effects. 2007. Vol. 30. №1. P.34–37.
4. Gatski M., Martin D.H., Theall K. Mycoplasma genitalium infection among HIV-positive women: prevalence, risk factors and association with vaginal shedding // STD AIDS. 2011. Vol. 22(3). P.155-157.
5. Goral J., Karavitis J., Kovacs E.J. Exposure-dependent effects of ethanol on the innate immune system // Alcohol. 2008. Vol.42. № 2. P. 237–247.
6. Hurley T.D., Edenberg H.J. Genes encoding enzymes involved in ethanol metabolism // Alcohol Res. 2012. Vol. 34. № 3. P.339–344.
7. Irving H.M., Samokhvalov A.V., Rehm J. Alcohol as a risk factor for pancreatitis. A systematic review and meta-analysis // Journal of the Pancreas. 2009. Vol.10. №4. P.387–392.

8. Lanzafame M., Ferrari S., Lattuada E. Mirtazapine in an HIV-1 infected patient with progressive multifocal leukoencephalopathy // Infez Med. 2009. Vol.17. №1. P.35–37.
9. Lönnroth K., Jaramillo E., Williams B.G. Drivers of tuberculosis epidemics: The role of risk factors and social determinants // Social Science & Medicine. 2009. Vol.68. №12. P.2240–2246.
10. Marty V.N., Spigelman I. Long-lasting alterations in membrane properties, k(+) currents, and glutamatergic synaptic currents of nucleus accumbens medium spiny neurons in a rat model of alcohol dependence // Frontiers in neuroscience. 2012. Vol. 6. P.86.
11. Rota M., Bellocco R., Scotti L. Random-effects meta-reg ression models for studying nonlinear doseresponse relationship, with an application to alcohol and esophageal squamous cell carcinoma // Stat Med. 2010. Vol. 29. № 26. P.2679–2687.
12. Salerno J., Darling-Fisher C., Hawkins N.M. Identifying Relationships Between High-Risk Sexual Behaviors and Screening Positive for Chlamydia and Gonorrhea in School-Wide Screening Events // Journal of School Health. 2013. Vol.83. №2. P.99–104.
13. Szabò I., Zoratti M., Gulbins E. Contribution of voltage-gated potassium channels to the regulation of apoptosis // FEBS Lett. 2010. Vol. 584. № 10. P.2049–2059.
14. Thode A.B. The Role of Multiple Hydrogen-Bonding Groups in Specific Alcohol Binding Sites in Proteins: Insights from Structural Studies of LUSH // Journal of Molecular Biology. 2008. Vol.5. № 7. P.1360– 1376.
15. Veazey R.S., Acierno P.M., McEvers K.J. Increased loss of CCR5+ CD45RACD4+ T cells in CD8+ lymphocyte-depleted Simian immunodeficiency virus-infected rhesus monkeys // Virol. 2008. Vol. 82. №11. P.618–620.
16. Wolen A.R. Genetic Dissection of Acute Ethanol Responsive Gene Networks in Prefrontal Cortex: Functional and Mechanistic Implications // PLoS ONE. 2012. Vol.7. №4. P.3–4.
17. Zeng J., Yang G.Y., Ying W. Pyruvate improves recovery after PARP-1-associated energy failure induced by oxidative stress in neonatal rat cerebrocortical slices // Cereb Blood Flow Metab. 2007. Vol.27. №2. P.304–315.
18. Zhang P.1., Bagby G.J., Happel K.I. Alcohol abuse, immunosuppression and pulmonary infection // Curr Drug Abuse Rev. 2008. Vol.1. №1. P.56–67.
19. Zhao H., Li T.T., Yin J.Y. Role of alcohol-metabolizing enzymes gene polymorphisms and environmental exposure on colorectal cancer: a case-only study // Zhonghua Liu Xing Bing Xue Za Zhi. 2013. Vol.34. № 10. P.1013–1017.
20. Morozov V.N., Galtsev A.S., Darmogray I.V., Morozova V.I., Khadartsev A.A., Darmogray V.N., Karaseva Yu.V. Diagnostics and treatment of chronic alcohol disease. 2004. № 9. P.80.
21. Morozov V.N., Khadartsev A.A., Karaseva Yu.V., Darmogray V.N., Morozova V.I., Galtsev A.S., Khapkina A.V. Course of frostbite against the background of alcohol intoxication. 2009. № 3. Pp. 211–213.