The 2\textsuperscript{nd} East-West Symposium on Biomedical Research of Alcohol-Related Diseases

Grodno, the Republic of Belarus, October 13-14, 2016
National Academy of Sciences of Belarus
Institute of Biochemistry of Biologically Active Substances
International Center on the Study of Alcoholism
European Society on Biomedical Research of Alcoholism

The 2nd East-West Symposium
on Biomedical Research
of Alcohol-Related Diseases

Grodno, the Republic of Belarus,
October 13-14, 2016

GRODNO, 2016
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В сборнике представлены программа и тезисы докладов симпозиума, организованного ГП “Институт биохимии биологически активных соединений НАН Беларуси” совместно с Европейским обществом по биомедицинскому изучению алкоголизма (ESBRA).
Dear Colleagues,

It is our great pleasure to welcome you to the “2\textsuperscript{nd} East-West Symposium on Biomedical Research of Alcohol-Related Diseases” here in Grodno. The Symposium will offer ample opportunities for productive discussions as well as possibilities to initiate new collaborations and joint projects among scientists from various countries all over the world. We would like to extend a warm welcome to all our invited speakers and thank them for their time and participation at this Symposium. We look forward to many scientific discussions throughout our meeting. We hope you will enjoy both the scientific and the social aspects of the Symposium.

On behalf of the Scientific and Organizing Committees of the 2\textsuperscript{nd} East-West Symposium on Biomedical Research of Alcohol-Related Diseases,

Vyacheslav Buko
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Symposium Venue

Conference hall, Institute of Biochemistry of Biologically Active Compounds, National Academy of Sciences, BLK-50, 230030 GRODNO, Belarus

Symposium Office

The Symposium Office will be open in the entrance hall of the Institute of Biochemistry of Biologically Active Substances, BLK, 50:

13.10.2016 - 0930 – 1730
14.10.2016 – 0830 – 1700
Costs

The symposium fee includes: registration, symposium materials and participation in extra activities/entertainments (coffee breaks and excursion). The payments will be made at the Registration Desk.

Lectures

Lectures will be delivered in English. A multimedia projector will be available for the presenters (presentation in MS Power Point).
SCIENTIFIC PROGRAM
Thursday, 13.10.2016

10⁰⁰ - 10¹⁵ OPENING CEREMONY

Zima T., President of the European Society on the Biomedical Research of Alcoholism, Rector of the Charles University, Prague, Czech Republic

Pronko P., Head of the International Center on the Study of Alcoholism, Deputy Director of the Institute of Biochemistry of Biologically Active Compounds, Grodno, Belarus

Plenary session

Chairpersons: Tomáš Zima, Prague; Vyacheslav Buko, Grodno

10²⁰ - 11⁰⁵ Zima T. (Institute of Medical Biochemistry and Laboratory Diagnostics, 1st Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic) Metabolism of alcohol and related health problems

11⁰⁵ - 11³⁵ Buko V. (Institute of Biochemistry of Biologically Active Compounds, Grodno, Belarus; School of Medical Sciences, Bialystok, Poland) Recent trends in the pharmacological treatment of alcoholic liver disease and its complications

Session I

Chairpersons: Yury Marakhouski, Minsk; Eleonora Patsenker, Zurich

11⁴⁰ - 12¹⁰ Patsenker E., Chicca A., Kellmann Ph., Mattson J., Brenneisen R., Semmo N., Gertsch J., Stickel F. (Department of Gastroenterology and Hepatology, University Hospital Zurich, Zurich, Switzerland; Department of Visceral Surgery and Medicine, Inselspital Bern & Department Clinical Research, University of Bern, Bern, Switzerland; Institute of Biochemistry and Molecular Medicine, University of Bern, Bern, Switzerland) Endocannabinoid system in chronic alcoholic liver disease

12¹⁰ - 12³⁰ Pronko P.S., Zimatkin S.M., Satanovskaya V.I., Khomich T.I., Shlyahtun A.H., Kandyba N.I., Kuvaeva Z.I. (Institute of Biochemistry of Biologically Active Compounds NAS of Belarus, Grodno, Belarus; Grodno State Medical University, Grodno, Belarus; Institute of Physico-Organic Chemistry NAS of Belarus, Minsk, Belarus) Arginine succinate and ethyl pyruvate have hepatoprotective action in chronically alcohol-intoxicated rats

12³⁰ - 12⁴⁰ Marakhouski Y.Kh. (Belarussian Medical Academy Postgraduate Education, Minsk, Belarus.) Efficacy infusion forms of essential branched-chain amino acids in alcoholic liver cirrhosis

13⁴⁰ – 13⁵⁰ Nundoo V., Karpiuk V.A., Voronko M.V. (Grodno State Medical University; Grodno Regional Clinical Center “Psychiatry-Narcology” Grodno, Belarus) Alcoholic liver diseases in patients of psychiatric clinics

13⁵⁰ - 14⁰⁰ Matsiyeuskaya N.V. (Grodno State Medical University, Grodno, Belarus) Influence of alcoholism on liver cirrhosis formation in HIV-positive patients
14:00–15:00 Lunch/Coffee break

Session II

Chairpersons: Pavel Pronko, Grodno; Nina Kanunnikova, Grodno

15:00–15:30 Konorazov I.I. (Ministry of Health, Minsk, Belarus) Prevention of alcohol abuse and alcoholism in Republic of Belarus: main achievements

15:30–16:00 Nemtsov A.V., Razvodovsky Y.E. (Institute of Psychiatry, Moscow, Russia; Grodno State Medical University, Grodno, Belarus) Was the alcohol-related mortality decline in Russia attributable to alcohol control policy?

16:00–16:15 Maksimchuk V.P. (Republican Research and Practice Center for Mental Health, Minsk, Belarus) Analysis of death courses among patients with addiction disorders

16:15–16:30 Razvodovsky Y. E. (Grodno State Medical University, Grodno, Belarus) Alcohol-related problems in Russia and Belarus: a comparative analysis

16:30–16:40 Shpakov A.A., Shlyahtun A.H., Shpakov A.I. (Yanka Kupala State University of Grodno, Grodno, Belarus; Institute of Biochemistry of Biologically Active Compounds, Grodno, Belarus; School of Medical Sciences, Białystok, Poland) Alcohol use among high school students: multicenter study


18:00 SYMPOSIUM DINNER
Session III

Chairpersons: Henriette Walter, Vienna; Marcin Wojnar, Warsaw

9:00-9:30 Walter H. (University Clinics of Psychiatry, Vienna, Austria) Pharmacotherapy of alcoholism

9:30-10:00 Wojnar M., Jakubczyk A. (Medical University of Warsaw, Department of Psychiatry, Warsaw, Poland; University of Michigan, Department of Psychiatry, Ann Arbor, MI, USA) Physical pain in alcohol-dependent patients entering treatment in Poland – prevalence, correlates and risk of post-treatment relapse

10:00 - 10:30 Vlasov V.V., Mulyukina N.A., Levitsky A.P., Gritsuk A.I. Natural grape products against alcoholism (National Research Centre “Tairov Institute of Viticulture and Wine Producing”, Odessa, Ukraine; Institute of Stomatology, Academy of Medical Sciences, Odessa, Ukraine; Gomel State Medical University, Gomel, Belarus)

10:30-10:45 Omelyanchik S.N., Borodina T.A., Semenovich D.S., Lukienko Ye.P., Shlyahtun A.H., Satanovskaya V.I., Kandyba N.I., Maksimchyk Y.Z., Gurinovich V.A., Pronko P.S., Moiseenok A.G. (Institute of Biochemistry of Biologically Active Compounds, NAS of Belarus, Grodno) Coenzyme A sequestration, glutathione system and alcohol metabolism enzymes under the treatment with valproic acid in conditions of alcohol intoxication

10:45-11:00 Gelberg I., Aleksa A., Wolf S., Avlasenko V., Artsukevich J., Tsiunchyk A., Masilevich A., Naumova N., Shejfer Y. (Grodno State Medical University, Grodno, Belarus) Clinical features and treatment efficacy in patients with a combination of multidrug-resistant tuberculosis and alcohol addiction

11:00-11:10 Sheibak V.M., Pavlyukovets A.Y., Nikolaev I.V., Doroshenko E.M., Smirnov V.Y. (Grodno State Medical University, Belarus) Alcohol intoxication and thymus free amino acids

11:10-11:20 Zavodnik I., Kirko S., Buko V., Maskevich A.A., Shlyahtun A.H. (Institute of Biochemistry of Biologically Active Compounds, Grodno, Belarus; Yanka Kupala Grodno State University, Grodno, Belarus) Application of cyclodextrin nanoconstructions for the treatment of alcoholic liver disease

11:20-11:30 Smirnov V.Yu., Razvodovsky Yu.E., Doroshenko Ye.M. (Grodno State Medical University, Grodno, Belarus) Free amino acids in blood plasma of rats undergoing alcohol exposure in different modes

11:30 – 12:00 Coffee break
Session IV

Chairpersons: Roberta Ward, London; Sergey Zimatkin, Grodno

12:00 – 12:45 Ward R. J. (Centre for Neuroinflammation & Neurodegeneration, Division of Brain Sciences, Imperial College London, United Kingdom) Alcohol-induced changes in systemic inflammation may induce activation of glial cells

12:45 – 13:05 Zimatkin C.M., Bon E.I. (Grodno State Medical University, Grodno, Belarus) Prenatal alcohol exposure affects brain cortex neurons postnatal development in rats

13:05–13:20 Phedina K.M., Paulava D.V. and Zimatkin S.M. (Grodno State Medical University, Grodno, Belarus) Brain histaminergic neurons in the conditions of single and repeated exposure to alcohol

13:20–13:30 Kanunnikova N.P. (Grodno State University, Grodno, Belarus; Institute of Biochemistry of Biologically Active Substances of National Academy of Science of Belarus, Grodno, Belarus) GABA catabolism modulation as a necessary component of a comprehensive metabolic therapy of alcohol intoxication and withdrawal

13:30–13:40 Shylahtun A.H., Buben A.L., Satanovskaya V.I., Kandyba N.I., Pronko P.S. (Institute of Biochemistry of Biologically Active Compounds, Grodno, Belarus; Grodno State Medical University, Grodno, Belarus) Central effects of betulin and betulin diacetate during ethanol withdrawal in rats

13:40–13:50 Lelevich V.V., Vinitskaya H., Lelevich S.V., Doroshenko E.M. (Grodno State Medical University, Grodno, Belarus) Levels of neuroactive amino acids and biogenic amines in brain are affected by intermittent periods of alcohol withdrawal

13:50–14:00 Khodos O.A. (Vitebsk State Medical University, Vitebsk, Belarus) Proteolysis in brain tissue and blood serum in chronic alcohol intoxication

14:00–14:10 Gritsuk A.I., Danchenko E.O., Kuhnovets O.A., Koval A.N., Petrenyov D.R. (Gomel State Medical University, Gomel, Belarus; Vitebsk State Pedagogical University, Vitebsk, Belarus; Institute of Radiobiology NAS Belarus, Gomel, Belarus) Blood serum ethanol could interfere with some ELISA of hormones

14:10–14:20 Yefimenko N.V., Dudok K.P., Sybirna N.O. (Ivan Franko Lviv National University, Department of Biochemistry, Lviv, Ukraine) L-arginine metabolism under alcohol intoxication: oxidative and non-oxidative pathways

CLOSING REMARKS

15:30 Guided tour: Old City of Grodno
INVITED LECTURES
METABOLISM OF ALCOHOL AND RELATED HEALTH PROBLEMS

Tomáš Zima

Institute of Medical Biochemistry and Laboratory Diagnostics, 1st Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic

Alcohol consumption goes through human beings, but high consumption was observed in the second half of the last century. Toxic effects of ethanol on the body are connected with its intake in large amounts. Alcohol organ injury is based on the direct effect of ethanol and also on its metabolites and produced compounds. There are four metabolic pathways of ethanol in the human body: alcohol dehydrogenase (ADH), the microsomal ethanol oxidizing system (MEOS, CYP2E1), catalase and a non-oxidative metabolism. Alcohol abuse is well-known for its liver damage. Alcoholic liver injury is accompanied by a wide spectrum of different diseases – steatosis, alcoholic hepatitis, alcoholic steatofibrosis/cirrhosis. The key mechanisms of liver injury are still not clear and we have focused on some of them, such as gender, genetic polymorphisms, immunologic, metabolic and nutritional factors.

Alcohol consumption and smoking are main factors of cancers in developed countries. The extrapolated data across Europe showed that 10% of all cancers in men and 3% of all cancers in women could be attributed to alcohol consumption. Australian data suggest that alcohol intake accounts to 5% of the total cancer burden of disease. Studies show that the risk of alcohol-related cancers is much higher in people who also smoke.

Alcohol is to develop the cancer via several mechanisms. Ethanol per se is a solvent for other carcinogens. The first metabolite, acetaldehyde, carcinogen, has a mutagenic effect on DNA via formation of DNA adducts and decreasing the activity of the DNA-repair system. Oxidation of ethanol produces reactive oxygen and nitrogen species with different effects on cells including their transformations, DNA and lipids damage. The changes in folate metabolism, alter methylation of DNA via ethanol and acetaldehyde by different metabolic pathways, and reduction of retionic acid influence cancer development. The mechanism of estrogen increasing in chronic alcohol consumption is not fully understood, but influences breast carcinogenesis. The effect of alcohol on cancer is modulated by polymorphisms in genes encoding enzymes for ethanol metabolism (e.g., alcohol dehydrogenases, aldehyde dehydrogenases, and cytochrome P4502E1) and for DNA-repair enzymes. The polymorphisms of ALDH2*1,2 a ADH1C*1 are associated with the risk of upper aerodigestive tract and colorectal cancers. The affection of the immune system (e.g., alcohol affects the B cell differentiation via down-regulation of the expression level of transcription factors and cytokine receptors) must be taken into the consideration while considering cancer development.

The chronic alcohol consumption is a world-wide social-economic problem and a major health issue including cancers, other alcohol-related diseases and addiction.

Acknowledgement: Supported by the research projects Prvouk P25/LF1/2 and MH CZ DRO VFN 64165.
Alcohol addiction is a chronic relapsing disease, which can be compared with diabetes, depression or high blood pressure. In the 1940s, two Danish scientists (Hald & Jacobsen, 1948) detected Disulfiram, as a medication blocking aldehyde dehydrogenase. Therefore it needs total abstinence. If alcohol is consumed, symptoms like tachycardia, flush, vomiting, and headache occur. In those days barbiturates were used to treat withdrawal syndromes. Only in the 60ies benzodiazepines made their way into treatment of withdrawal. Later naltrexone was introduced in the field of alcohol, which is known to reduce the amount of drinking, and which works very well in types III and IV according to Lesch. Next to come was the antiglutamatergic acting acamprosate, an anti-craving substance. Benzodiazepines frequently led to benzodiazepine addiction, if anti-withdrawal medication was not tapered off. Dosages of benzodiazepines were increased or it was taken together with alcohol. Relief could be use of gamma-hydroxybutyric acid, an easily produced liquid, taken orally, which reduces the withdrawal symptoms. Because of its narcotic status it is not so easy to get similar to the benzodiazepines. Nalmefene, another opioid antagonist and Baclofen, a muscle relaxant, are the two promising newcomers in alcoholism treatment. Baclofen, which was, in 2014, in France liberated from its “off label use” status for 3 years, has been widely studied, showing positive and negative effects. New studies will decide upon its future. There are many more substances, but the above mentioned constitute the 6 pillars of today’s pharmacotherapy in Europe.

References:


ALCOHOL-INDUCED CHANGES IN SYSTEMIC INFLAMMATION MAY INDUCE ACTIVATION OF GLIAL CELLS

Roberta J. Ward

Centre for Neuroinflammation & Neurodegeneration, Division of Brain Sciences, Imperial College London, United Kingdom

Alcohol-induced neuroinflammation occurs in both chronic and intermittent alcohol abusers. While animal studies have indicated a pro-inflammatory milieu in specific brain regions after intermittent alcohol abuse, (a M1 microglial phenotype) to what extent this is induced in chronic alcohol abuse remains unclear. Some studies have reported increased levels of systemic pro-inflammatory cytokines in the plasma of chronic alcohol abusers but it is unknown whether this reflects glial activation. Such inflammatory mediators together with activated monocytes and lymphocytes can cross the blood brain barrier to trigger glial activation which can alter synaptic plasticity and contribute to cognitive dysfunction and depression. The source of the plasma inflammatory mediators remained undefined.
PHYSICAL PAIN IN ALCOHOL-DEPENDENT PATIENTS ENTERING TREATMENT IN POLAND – PREVALENCE, CORRELATES AND RISK OF POST-TREATMENT RELAPSE

Marcin Wojnar 1, Andrzej Jakubczyk 2

1Medical University of Warsaw, Department of Psychiatry, Warsaw, Poland
2University of Michigan, Department of Psychiatry, Ann Arbor, MI, USA

Background and aims: Chronic pain and harmful alcohol use commonly co-exist, as the use of alcohol is commonly considered a useful pain self-management strategy. Moreover, physical pain has been considered a potential predictor of relapse in alcohol-dependent individuals after treatment. However, it is not clear how presence of pain may interact with other known triggers of return to drinking and whether reduction of pain would decrease risk of post-treatment relapse in alcoholism. The purpose of this study was to characterize pain and pain-related problems in a group of primary alcohol-dependent individuals entering treatment facilities and to examine if changes in experience of pain before and after the treatment influence risk of post-treatment relapse to alcohol use.

Methods: A sample of 366 (73.5% men and 26.5% women) alcohol-dependent (according to DSM-IV criteria) subjects was recruited in alcohol treatment centers in Warsaw, Poland. Information was obtained about demographics, social functioning, sexual and physical abuse during childhood, and severity of alcohol and sleep problems as well as level of pain, impulsivity and general psychopathology. After completing alcohol treatment program patients were followed up for 12 months and alcohol use, including relapse, as well as pain severity were evaluated.

Results: Among the study group, 34.4% of the individuals reported moderate or greater physical pain during the last 4 weeks. Experience of physical pain was significantly associated with lower level of education, unemployment, experience of childhood sexual abuse, and severity of alcohol dependence as well as other potential predictors of relapse (impulsivity, sleep problems, general psychopathology). When entered into logistic regression analysis with other dependent variables, the level of general psychopathology, severity of sleep problems, age, and education were all significantly associated with pain severity. At the follow-up assessment, 29.5% of the patients confirmed that they drank alcohol during last four weeks. Comparing to the baseline pain levels, 48.6% of subjects reported increased severity of pain, 28.8% – comparable levels, and 22.6% of alcoholics declared decreased severity of pain after treatment. There was a significant association between the decrease in the level of pain and the lower risk of relapse. Other factors associated with relapse during four weeks prior to the follow up were: baseline severity of depressive symptoms, low social support at baseline and number of drinking days during 4 weeks prior to entering treatment. In multivariate analysis, a decrease in pain level was associated with a lower likelihood of relapse (OR=0.159; 95%CI:0.04-0.62; p=0.008) even when controlled for other factors associated with relapse.

Conclusions: Physical pain is a prevalent and potentially impairing experience in adults seeking treatment for alcohol dependence. The study on a treatment sample of alcohol-dependent individuals indicates that decreases in pain level following treatment for alcohol dependence are associated with, and may contribute to, a lower risk of alcohol relapse. Therapeutic interventions aimed at reducing pain in alcohol-dependent individuals should be studied to evaluate their impact on improving overall treatment outcomes.
ENDOCANNABINOID SYSTEM IN CHRONIC ALCOHOLIC LIVER DISEASE

Patsenker E. 1, 2, Chicca A. 3, Kellmann Ph. 2, Mattson J. 2, Brenneisen R. 2, Semmo N. 2, Gertsch J. 3, Stickel F. 1

1Department of Gastroenterology and Hepatology, University Hospital Zurich, Zurich, Switzerland, 2Department of Visceral Surgery and Medicine, Inselspital Bern & Department of Clinical Research, University of Bern, Bern, Switzerland, 3Institute of Biochemistry and Molecular Medicine, University of Bern, Bern, Switzerland

Introduction: Cannabinoid receptors CB1 and CB2 are implicated in the development of chronic liver diseases. However, the mechanisms by which the endocannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG) contribute to ongoing liver damage in alcoholic liver diseases (ALD) are incompletely defined.

Methods: Anandamide and 2-arachidonoylglycerol were measured by gas chromatography and mass spectrometry (GC-MS) in plasma from healthy individuals and ALD patients. Gene expression was assessed by TaqMan PCR. In vivo, liver fibrosis was induced by combination of ethanol and CCL4 for 5 weeks in C57BL6 mice, which were treated with inhibitors of fatty acid amid hydrolase (FAAH, URB937), monoacyl glycerol lipase (MAGL, JZL184) or vehicle control for 4 weeks. Liver damage was assessed by ALT and AST levels and histology. Collagen content was measured by hydroxyproline determination and Sirius Red stain. Hepatic inflammation and necrosis were evaluated from H&E stainings.

Results: AEA and 2AG plasma levels were significantly higher in patients with ALD, whereas FAAH and MAGL mRNA in liver biopsies were 2- and 10-fold downregulated, respectively, compared to healthy controls. Statistical analysis revealed ALT, AST and alcohol levels as predictors of high AEA among alcoholic patients (p<0.05). The active metabolite of ethanol - acetaldehyde (AA) slightly inhibited enzymatic activity of MAGL, reflected by a reduced amount of hydrolyzed 2AG. In peripheral blood mononuclear cells, AA showed similar effect by reducing MAGL mRNA. In vivo, inhibition of FAAH and MAGL by URB937 and JZL184 in alcohol-induced liver injury in mice did not affect strongly liver fibrosis, inflammation and necrosis, but modified fibrosis- and inflammation-related gene expression. Instead, CB2 agonist MHK significantly improved mouse survival, and slightly alleviated hepatic fibrosis, necrosis and inflammation. MHK induced the expression of MMP-2, -3, -9 and -13, while strikingly downregulated the expression of CB1. Treatment with MHK normalized the levels of Mcl-1, JNK1 and of necroptotic RIPK1. In addition, MHK elevated the levels of endocannabinoids and fatty acids in the liver, paralleled by downregulation of fatty acid synthase (FAS) and diacylglycerol O-acyltransferase 2 (DGAT2) expression and PNPLA3 induction.

Discussion / Preliminary conclusion: Chronic alcohol consumption induces endocannabinoids AEA and 2AG levels possibly via the blockage of endocannabinoid degradation enzymes activity. Whether this elevation actively contributes to the ongoing alcohol-related liver damage still remains to be elucidated in more details. CB2 agonism by MHK increased survival and revealed hepatoprotective properties via modulation of matrix remodelling and regulating lipid metabolism, proving CB2 as a promising therapeutic target in chronic liver diseases.
ABSTRACTS
RECENT TRENDS IN THE PHARMACOLOGICAL TREATMENT OF ALCOHOLIC LIVER DISEASE AND ITS COMPLICATIONS

Buko V.

Institute of Biochemistry of Biologically Active Compounds, Grodno, Belarus; School of Medical Sciences, Bialystok, Poland

Development of new approaches to treatment of alcoholic liver disease (ALD) and its consequences (fibrosis/cirrhosis, portal hypertension, etc.) still remains urgent. It is possible to define from these approaches a search for new hepatoprotectors and antifibrotics based on synthetic or plant-derived substances, combination therapy and application of nanoconstructions to enhance the efficacy of proven medicines.

Ursodeoxycholic acid (UDCA) is a hepatoprotector widely used in the clinics. Our investigations as well as the data from other laboratories suggested anti-inflammatory, antifibrotic and immunomodulating properties of this compound. We studied the pharmacological effects of UDCA homologs with a shortened carbon chain in experimental models of alcoholic steatohepatitis and liver fibrosis induced by thioacetamide (TAA). It has been shown that homologs, in particular nor-UDCA, considerably surpass the parental substance in hepatoprotective and antifibrotic properties.

As our own data suggested, a significant hepatoprotective effect among plant-derived substances, besides the well-known silymarine, was manifested by other compounds, such as borage oil, extracts of red cabbage and cranberry, as well as betuline. These substances, being low cost and non-toxic, can be used in the clinics for treatment of alcoholic steatohepatitis.

Combination of the proven and potential hepatoprotective and antifibrotic agents with that show different actions is most promising. This will make it possible to use lower, non-toxic amounts of single agents for treatment. These combinations, once effective in suitable experimental models in vivo, can be easily tested in a clinical setting, since most of the single agents have a satisfactory clinical safety profile. We demonstrated high hepatoprotective and anti-inflammatory activities of different drug combinations in rat alcoholic steatohepatitis: silymarin and essential fatty acids, UDCA and pentoxifylline, UDCA and betaine. Using TAA-induced model of liver fibrosis we studied combinations of promising antifibrotics (simvastatin, losartan, pentoxifylline, mycophenolate mofetil, interferon α, pioglitazone). We found that the combinations had higher antifibrotic activities than monopreparations used in an appropriate combination.

Application of hepatoprotectors combined with cyclodextrine nanoparticles enhanced solubility of sparingly soluble substances and consequently their bioavailability. Our preliminary studies suggested that nanocombination of plant-derived hepatoprotectors (betuline, cranberry extract) increased their pharmacological activities in experimental alcoholic steatohepatitis.
EFFECT OF ALCOHOL ABUSE ON THE CHARACTER OF THE PROCESS IN PATIENTS WITH MULTIDRUG-RESISTANT TUBERCULOSIS


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Multiple-drug resistant tuberculosis (MDR-TB) - TB is caused by mycobacteria that are resistant to two or more anti-TB drugs, including rifampicin and isoniazid, the most active medicines against Mycobacterium tuberculosis (MTB). It is characterized by more severe course and relatively low efficiency of the therapy.

400 patients with MDR-TB hospitalized for 2011-2015 yrs. in the Grodno Regional Clinical Center “Phthisiatry” were examined: 221 suffered from alcohol abuse (1st group) and the 2nd group included 179 patients without alcohol addiction. The first group included more men - 85.1% and 74.3%, respectively (p <0.05). There was no significant difference in age. Fibrous-cavernous tuberculosis was more common in the first group (18 patients -8.1% versus 4 pts. - 2.7%), whereas decay cavities occurred in 131 pts. (59.3% vs. 73 pts. - 40, 8%, p <0.05) and chronic forms of disease - in 21 patients (9.5%) vs 5 pts. (2.8%), p <0.05. Clinical manifestations of tuberculosis intoxication (fever, weakness, malaise, sweating, weight loss, etc.) were significantly more common in patients of the 1st group 178 (80.5%) than in patients of the second group: only 96 (53.6%), p <0.05. Risk factors were absent in 48 (26.8%) patients who did not abuse alcohol. All patients of the first group had one or more risk factors (p <0.05). The gastrointestinal tract and liver diseases (21.3% vs. 10% and 9.9% vs. 2.8%, respectively, p <0.05) were noted more often in the first group, as compared to the second one. The number of persons with imprisonment in history amounted to 43 (19.4%) in the first group vs. 9 (5.0%) in the second one, p <0.05. A significant difference in the groups was in the level of non-performing - 69.1% and 28.2% of the number of working age (p <0.01), as well as people with disabilities - 9.9% versus 2.8% (p <0.05).

Thus, the abuse of alcohol has a strong negative effect on the original character and manifestation of tuberculosis process in MDR-TB patients.
BLOOD SERUM ETHANOL COULD INTERFERE WITH SOME ELISA OF HORMONES

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Studying of alcohol intoxication-derived endocrine and metabolic disorders by biochemical blood parameters can be used to develop criteria for assessing the degree of intoxication severity. But blood ethanol in intoxicated patients can influence the specificity of detection and biochemical parameters. Despite the obvious urgency of this problem, it is poorly understood.

The aim of the study was to determine the effect of various serum ethanol concentrations for measuring the contents of proinsulin, C-peptide, insulin, leptin, triiodothyronine (T3) and cortisol and to assess its effect on the analytical procedure specificity.

We studied the drain serum, for which the serum remained collected in a single container for a week and the tubes stored at -20°C. After accumulating up to a volume of 100 ml it was thawed in a water bath at 37°C, thoroughly mixed and filtered through a sterile filter, poured into 10 ml vials, and stored at -20°C. Before starting the study, the serum was thawed and a 2\% ethanol solution added in the amounts of 0.15, 0.53, 1.11, 2.5 and 4.29 ml to give the final concentrations of 0.3, 1.0 ethanol, 2.0, 4.0 and 6.0 \(\%\) (g/l). The corresponding blood serum dilutions were 1.01-, 1.05-, 1.11-, 1.25- and 1.43- fold without protein denaturation. These samples were tested in triplicate, the original serum served as control. The content of these hormones was determined by enzyme immunoassay kits (ELISA) from DRG International Inc. (USA). Exogenous ethanol did not affect the specificity of cortisol and insulin. However, in the presence of serum ethanol the results of T3 and leptin ELISA may be distorted because with increasing blood alcohol level T3 was progressively decreased significantly, whereas leptin concentration increased. A significant overestimation of proinsulin content and reduced C-peptide were observed at the serum ethanol level of 4 and 6 g/l, despite its 1.25- and 1.43-fold dilution respectively. 64.3\% - reduced C-peptide detectability at the 6.0 g/l serum ethanol concentration can be explained by serum dilution. However, only 21.3\% of blood serum T3 detectability was due to the direct influence of ethanol on the ELISA procedure. Proinsulin and leptin detectability increases, respectively, to 153.8\% and 123.6\%, which is based on the dilution of serum. Taking into consideration the dilution of serum, the ethanol effect was more pronounced. The negative effect of ethanol on the ELISA hormones in blood may be caused by disturbance in the ligand-protein relationships in the systems of antigen-antibody, ligand-receptor, substrate-enzyme, causing diagnostic errors due to distortion of the actual concentration of hormone and metabolites and enzyme activity.
GABA CATABOLISM MODULATION AS A NECESSARY COMPONENT OF COMPREHENSIVE METABOLIC THERAPY OF ALCOHOL INTOXICATION AND WITHDRAWAL

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It has been demonstrated that the processes of energy formation and activity of the GABA system in the brain are depressed following ethanol administration. Consequently drugs acting on the GABA shunt activity and a structure close to natural metabolites may be useful in metabolic therapy of alcohol intoxication. We studied the influence of some substances, which had structures similar to that of GABA (gamma-butyrolactone, glutamine, gopanthene) or which changed activities of its metabolizing enzymes (valproic acid, ethanolamine, phosphoethanolamine), on the GABA metabolism disturbances in brain structures caused by alcohol intoxication and withdrawal. It is known that hydroxybutyrate and gamma-butyrolactone reduce abstinence symptoms and alleviate craving for alcohol consumption as successfully as acamprosate or naltrexone (Keating, 2014; Caputo et al., 2015). Sodium valproate and glutamine are used for treatment of alcohol abstinence (Burov, Vedernikov, 1986; Rogers et al., 1956). Ethanolamine and phosphoethanolamine affect the metabolic pathways of ethanol (Ostrovsky et al., 1988). Gopanthene is used for alcohol intoxication treatment (Kanunnikova et al., 1998). We showed that all the above substances diminished behavioural effects of ethanol and ethanol-induced disturbances of the GABA catabolism, especially its oxidative path. These changes were pronounced in the brain stem. Diminution of the alcohol-induced changes was observed in the case when the direction, associated with effects of the drugs, coincided with the ethanol effects.

Studying of the GABA-ergic substance effects during chronic alcohol intoxication and subsequent alcohol withdrawal when disturbances in the GABA catabolism were most pronounced showed that the majority of the examined substances — sodium valproate, glutamine, gamma-butyrolactone, gopanthene — diminished the disturbances in the GABA metabolism in the brain structures that had developed during alcohol withdrawal. The most effective modulators of the ethanol-induced GABA metabolism disorders were gamma-butyrolactone, gopanthene and sodium valproate.

Hence, our data confirm the effectiveness of the above compounds for correction of disorders caused by chronic alcohol intoxication and the subsequent withdrawal. Our data allow us to recommend GABAergic modulators as a necessary component in the comprehensive metabolic therapy of alcoholic intoxication and withdrawal.
PROTEOLYSIS IN BRAIN TISSUE AND BLOOD SERUM IN CHRONIC ALCOHOL INTOXICATION

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This study was undertaken to determine the activity of trypsin-like and cysteine proteinases and their endogenous inhibitors in brain tissue and blood serum in Wistar male rats with chronic alcohol intoxication. A 15% ethanol solution was given for experimental animals during 29 weeks. Water was given for animals of the control group. Proteinases and their endogenous inhibitors activities in cerebral hemispheres and cerebellum tissue were studied spectrophotometrically. The substrate was N-α-benzoyl-D,L-arginine-p-nitroanilide (BAPNA). The results of our study indicate changes in the activity of trypsin-like proteinases in the brain tissue in chronic alcohol intoxication. Our findings suggest that chronic alcohol intoxication upsets the normal physiological balance of the activity of trypsin-like and cysteine proteinases and their endogenous inhibitors in cerebral hemispheres and cerebellum tissue. It was found that the changes in proteinases and inhibitors activities were most expressed on the first and third days of alcohol withdrawal. The disorders in proteolysis were also observed in blood serum. It was revealed that chronic alcohol intoxication was accompanied by decreasing of α1-proteinase inhibitor and α2-macroglobulin activities. Normalization of the physiological balance of the activities of proteinases and their endogenous inhibitors in brain tissue and blood serum was not attained even in 7 days after alcohol withdrawal.
PREVENTION OF ALCOHOL ABUSE AND ALCOHOLISM IN REPUBLIC OF BELARUS: MAIN ACHIEVEMENTS

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The abstract is not presented.
According to WHO statistics, alcohol consumption is the third leading cause of death, after malignant neoplasms and cardiovascular disorders. The number of deaths from all causes among those who misuse alcohol, 2 - 4 times higher than in general population. The frequency of alcohol dependence in male patients hospitalized for various reasons is 4.8 - 45%.

We analyzed indicators of mortality in the Republic of Belarus for the period of 2006-2013 years due to diseases and pathological conditions occurring as a result of alcohol misuse: alcohol dependence; alcohol use related psychotic disorders, encephalopathy, dementia; alcoholic cardiomyopathy; alcoholic liver diseases (cirrhosis, hepatitis, fibrosis); alcohol poisoning. The proportion of number of deaths whose main cause was reported to be one of the listed above diseases was 3.0% of the total number of deaths during this period. The average annual mortality associated with alcohol misuse, for the period of 2006-2013 equals to 41.67 per 100 thousand general population, with 59.5% of deaths associated with alcohol poisoning (24.79 per 100 thousand general population), 15.2% - for alcoholic liver disease (cirrhosis, hepatitis, fibrosis) (6.32 per 100 thousand general population), 13.4% - alcohol dependence (5.59 per 100 thousand general population), 10.1% - alcoholic cardiomyopathy (4.22 per 100 thousand general population), 18% - alcohol use related psychotic disorders, encephalopathy, and dementia (0.74 per 100 thousand people).

Alcohol misuse significantly contributes to the working age population mortality. The mortality rate of the working age population makes 9.6% of the total number of deaths accounted for causes related to hazardous alcohol use. The average annual mortality associated with alcohol consumption, was 50.09 per 100 thousand, whereas in working-age population was represented an increase of 20.2% in the general population. In the structure of mortality in the working age population the proportion of alcohol poisoning was 61.6% (30.84 per 100 thousand general population), alcoholic liver disease - 13.5% (6.75 per 100 thousand general population), alcohol dependence - 12.5% (6.26 per 100 thousand general population), alcoholic cardiomyopathy - 10.6% (5.32 per 100 thousand general population), alcohol use related psychotic disorders, encephalopathy, and dementia - 1.8% (0.92 per 100 thousand population).

The analysis shows the need to develop effective methods of both prevention of alcohol use related disorders and comprehensive rehabilitation of patients with these disorders.
Acute alcohol intoxication (AAI) is characterized by inhibition of glycolysis and pentose phosphate pathway (PPP) in the liver, which is mainly manifested after administration of high ethanol doses. Inhibition of glycolysis in AAI may be caused by a hormonal imbalance – depression of the level of insulin and rising of endocrine activity of the thyroid gland. Thus, AAI slows down glucose catabolism, and, therefore, the energy producing processes in a liver. Chronic alcohol intoxication (ChAI) for 14 days did not significantly change glucose catabolism in glycolysis and PPP in the liver. It is in accordance with the normal level of insulin and thyroxin in blood serum. The elongation of the alcoholization period for up to 28 days was followed by retardation of glycolysis and PPP while the levels of insulin, T3 and T4 were lowered. However, these effects were pronounced to a lesser extent compared to severe AAI. Alcohol withdrawal (AW) (1 day) was followed by inhibition of glucose catabolism in liver, which is comparable with the same effect in 28-day ChAI. After three days of abstinence, normalization of glycolysis and PPP functional activities was more pronounced and the latter effect was observed when at the normal level of insulin. Therefore, the disturbances in the metabolism of glucose in the liver at the remote periods of abstinence were not caused by hormonal imbalance, but induced by other regulatory mechanisms. Such an effect can develop further at least in two directions. First, it can lead to formation of a low energy state in this tissue. Second, there has to be a switching of cells to utilization of other substrates, which involves adaptive changes in the turnover of lipids and other components. All this can lead to formation of the so-called “narcomaniac” homeostasis which is shown in abuse of different types of drugs.
LEVELS OF NEUROACTIVE AMINO ACIDS AND BIOGENIC AMINES IN BRAIN ARE AFFECTED BY INTERMITTENT PERIODS OF ALCOHOL WITHDRAWAL

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Rodent models of the alcohol-dependent state indicate that a withdrawal reaction can be produced whenever intoxication has been continuously maintained, even for short periods of time. The development of the tolerant/dependent state resembles a physiological adaptation in two ways. Firstly, the animal is no longer much affected by the drug, and secondly, withdrawal reveals a condition of CNS hyperexcitability that is the opposite of the primary drug effect. Our study was aimed to compare the effects of different types of alcohol withdrawal (AW) on the levels of biogenic amines (serotonin, dopamine, norepinephrine), their metabolites, and neurotransmitter amino acids (GABA, glutamate, aspartate, glycine) in several rat brain regions (cortex, midbrain, thalamus, striatum).

In 14-day discontinuous alcohol intoxication (DAI), rats underwent 2 cycles of intragastrical administration of 25% ethanol solution (3.5 g/kg, twice, daily for 4 days), followed by 3-day alcohol-free periods. In the severe AW model, the duration of alcohol administration to rats increased to 5 days and the daily dosage of ethanol was 5 g/kg of body weight. The levels of biogenic amines and amino acids were measured in the rat brain regions 1 and 3 days after the last ethanol administration (1-day and 3-day AW).

The changes in the contents of dopamine and serotonin, their metabolites and free amino acids varied depending on the duration of alcohol intoxication and the brain region tested. The 14-day DAI led to a significant increase in the levels of dopamine and serotonin in the striatum, and that effect was attenuated 1 and 3 days after severe AW.

The highest growth of dopamine level was noted in the cortex, midbrain and thalamus of rats 1 day after severe AW, indicating higher activity of dopaminergic neurons and possible CNS hyperexcitability. However, 3-day AW was followed by less pronounced changes in the levels of dopamine and its metabolites. The serotonin level was higher in cortex one day after AW, and did not change in 3-day alcohol cessation.

It was proposed that the changes observed may occur due to non-specific adaptation of neurons to the excessive alcohol consumption and further cessation. The results obtained on the levels of biogenic amines and their metabolites in the brain may form a basis for a rational picture of the biochemical changes responsible for the withdrawal syndrome.
ANALYSIS OF DEATH CAUSES AMONG PATIENTS WITH ADDICTION DISORDERS

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Introduction. Mortality rate of the population depends on many factors including material well-being, quality and availability of medical care, awareness of the value of life and proper attitude towards one’s own health and the environment.

Objective. The main purpose of the present study was to elucidate the causes of death among out-patient subjects with addictive disorders and to develop preventive measures against mortality in this group of patients.

Research methods. The main method used in this study was exploring the statistical indices of health care organizations that have been providing narcological help in dynamics for the last 8 years.

Results and discussion. The general mortality of the population of the Republic of Belarus has decreased by 10.3% for the last 8 years (2008-2015) and the number of subjects who died from external reasons during that period of time has decreased by 39.8%. The level of alcohol use has reduced by 27.0% (from 12.39 l. absolute alcohol per capita to 9.05 l.) for the last 8 years. Total number of subjects taken off the narcological register due to their death in 2015 accounted for 4249, which represents 2.4% of all out-patient subjects with addictive disorders. The main cause of death in the indicated group of patients – cardiovascular disorders (56.1%), the second place by the rate is taken by liver diseases (4.3%). It was shown that the greatest mortality among out-patient subjects is observed at the age of 41-59 years (on average 57.8% of patients die annually), the second place takes the age interval of 31-40 years (18.6%) and over 60 years (18.2%), only 5.4% of subjects die annually at the age of 18-30 years.

Conclusions. Reducing the rate of mortality related to alcohol use will allow to lower significantly the level of general mortality, thus it is necessary to improve the quality of diagnostics of alcoholic mortality and to improve the availability of medical care to all segments of the population.

In order to prevent mortality among out-patient subjects with addictive disorders the following measures are reasonable:
1. To conduct epidemiological studies on the rates of alcohol consumption in the Republic of Belarus constantly.
2. To analyze annually the data on the number of patients with addictive disorders treated in in-patient hospitals and the data on primary requests for medical care in psychiatric or narcological organizations.
3. In order to provide individual prophylaxis, it is necessary to carry out work on development in each single patient the system of principles and skills aimed at prevention of poisonings from alcohol and its substitutes and prevention of dependence.
EFFICACY OF INFUSION FORMS OF ESSENTIAL BRANCHED-CHAIN AMINO ACIDS IN ALCOHOLIC LIVER CIRRHOSIS

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A large-scale (sample of 720 cases) multicenter (7 centers), national, post-registration, retrospective and prospective, comparative, partially randomizing, with following up, and explanatory clinical study of infusion forms of essential branched-chain amino acids (BCA Ainf / Hepavil ) to evaluate their efficacy and safety in chronic liver diseases (CLD) was performed in Belarus.

Method. The alcoholic liver cirrhosis (ALC) group was selected from 720 cases with CLD by using calculation ANI index. Patients with ANI of +5.0 or more were selected as ALC (n = 40), whereas those with ANI index of -5 or less were classified in the subgroup of non-alcoholic cirrhosis (NALC)(n = 36).

In ALC mean age - 52.7 years (95% CI = 48.9-56.7, median - 50.5 (95% CI = 48-58) versus - 55.8 years (95% CI = 51.9-59.8), median - 57 (95% CI = 50-61) in NALC. There were no significant differences in the values of BMI and gender ratio. Thus, these subgroups were homogeneous in baseline characteristics. BCA Ainf infusion duration in ALC was 10.5 days (95% CI = 9.5-11.6, median - 10 (95% CI = 8-12), NALC - 9.2 days (95% CI = 8.0-10.3, median - 8 (95% CI = 7-9). By the primary effectiveness outcome point was the blood albumin content changes before and after treatment.

Results. Comparison the frequency occurrence of the values in blood albumin 35 g / l or higher in the subgroup of NALC gave the following results: before treatment – 11.8%, after - 47.1% (Ptrend = 0.003). Odds ratio (OR) frequency higher albumin values after treatment – 6.67 (95% CI = 1.96-22.7), and NNT is 2.2 (95% CI = 1.8-7.8).

A similar analysis for subgroups ALC showed the following results: before treatment - 7.5%, after - 53.9% (Ptrend = 0.00001). OR for the treatment to increase blood albumin was 14.4 (95% CI = 3.9-53.7), and NNT was 2.2 (95% CI = 1.6-4.0).

In cirrhosis-C, it was shown that the treatment significantly reduced the occurrence frequency (share in %) of high mortality prognostic index during the year: OR reduction of the incidence of predictive deaths was 4.5 (95% CI=1.7–10.4) (Ptrend=0.012), i.e., the use of BCAA infusion reduces by 4.5 times the incidence of higher risk death in cirrhosis-C.

Conclusion. Essential branched-chain amino acids infusion (duration 10 days) in alcoholic liver cirrhosis demonstrated positive effectiveness by albumin contents in blood and mortality prognostic index during the year.
Liver pathology is one of the leading causes of death in HIV-infected patients globally. The “liver" mortality rate has achieved 14-18% in patients receiving antiretroviral therapy. The liver pathology has a combined nature as a result of simultaneous action of different hepatotoxic factors (alcohol, viruses, drugs, and intravenous drugs use (IDU)). Alcoholism (AL) is widely distributed among HIV-positive persons all over the world.

**Aim of study:** to estimate the role of alcoholism on liver cirrhosis formation in HIV-infected persons.

**Material and methods.** Clinical and pathomorphological data of dead 119 HIV-infected patients in the period from 2004 to 2010 were analyzed. Among them females were 34 (28.6%), males - 85 (71.4%), with the mean age of 35.6±6.68 years. Only patients with established history of hepatotoxic factors: alcoholism (AL), intravenous drugs use (IDU), and co-infections of hepatitis C virus (HCV) or hepatitis B virus (HBV) were included in study. The program “STATISTICA 10” was used for statistical analysis.

**Results.** Liver cirrhosis (LC) was diagnosed in 35 (28.6%) patients in the group, hepatitis of high and moderate activity with different stages of liver fibrosis was established in 38 (31.9%) ones. Hepatitis of minimal activity (HMA) with fibrosis of 0-1 stages (according to Knodell) was in 43 (36.1%) patients. In 3 cases, acute toxic hepatitis with high activity occurred. Among patients with liver cirrhosis (LC) the frequency of AL was significantly higher in comparison with patients with HMA: 25 (71.4%) and 9 (20.9%), respectively (p<0.05), OR (AL for LC formation) was 9.4 (95% CI: 3.34-26.7). The frequency of HCV co-infection did not differ significantly in patients with LC and HMA: 33 (94.3%) and 37 (86.0%), respectively (p>0.05). The frequency of combined AL and HCV co-infection was significantly higher in patients with LC in comparison with patients with HMA: 13 (37.1%) and 2 (4.7%), respectively (p<0.05), OR – 12.1 (CI: 2.5-58.59). The frequency of combined AL, HCV co-infections and IDU was significantly higher in patients with LC as compared to patients with HMA: 12 (34.3%) and 6 (14.0%), respectively (p<0.05), OR – 3.22 (CI: 1.06-9.76).

**Conclusions.** Alcoholism in combination with HCV co-infection and IDU are factors strongly associated with liver cirrhosis formation in HIV-infected patients.
Was the Alcohol-related Mortality Decline in Russia Attributable to Alcohol Control Policy?

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Turbulent events of the last 10 years on the Russian alcohol scene became the subject of special attention in the expert community. A coincidence in the alcohol consumption and alcohol-related mortality trends allows several experts to hypothesize that the reduction in the number of alcohol-related deaths during the last decade might be attributed to the implementation of the alcohol policy reforms in 2006, which increased government control over the alcohol market. Anti-alcohol activity in Russia began with the adoption of two laws in 2005. The first one (102—FL), among other issues, introduced new excise stamps from January 1, 2006. After that time, other stamps have been prohibited. The second law (209—FL) significantly increased nominal capital of alcohol market players since July 1, 2006, so that the market became free from small and average players in favor of large producers. Moreover, the law 209 introduced new and more toxic denaturant additives for household alcohol-containing liquids after July 1, 2006. The introduction of new excise stamps has been a routine procedure: since 1994, they have been changed seven times (1994, 1996, 1997, 1998, 2001, 2003 and 2005) and differed only in their protection level. There was a significant delay with their printing: first stamps were issued in February 2006 only for 0.5l vodka bottles. Stamps for other beverages were printed during the year. This resulted in long and complex market disorganization. In addition, since July 1, chaos had increased because small producers and distributors left the market. Naturally those changes were accompanied by both consumption and mortality rate decrease in 2006–2007. One of the consequences of the legal alcohol shortages was appearance of additional amounts of toxic ‘alcohol substitutes’ on the market, for example household chemistry liquids with new denaturant additives. The latter led to an increase of toxic hepatitis incidence and elevated mortality rates due to liver diseases in the following years. By 2008, the crisis in the alcohol market was overcome, and mortality rates returned to the 2004–2005 trends. Therefore, the effect of the policy measures introduced in 2006 was rather a side effect of the two laws characterized by numerous negative consequences. It is highly probable that this decrease was based not on the direct action of the laws of 2005, but rather on negligent execution of these laws and subsequent chaos on the alcohol market. As a result, the fast decrease in alcohol-related mortality rates in 2006–2008 was a side effect of this chaos provoked by the laws of 2005. Highly important for the decrease in alcohol consumption and connected mortality was the forced elimination of mid-level and small market participants in mid-2006. However, large-scale alcohol business had compensated for this loss by 2008. One cannot completely rule out the influence of the laws in question on the decrease of mortality in the country, but it is almost impossible to separate this influence from other factors. In conclusion, it seems plausible that alcohol policy has a very weak influence on the alcohol situation in Russia.
ALCOHOLIC LIVER DISEASES IN PATIENTS OF PSYHIATRIC CLINICS

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In general practice from 20% to 40% of patients have disorders associated with alcoholism. The damage of the internal organs may be the first and sometimes the only manifestation of alcohol abuse, with a predominance of visceral disorders in psychopathology. Alcohol-induced damage to the internal organs is not obligatory, it is not absolute and dose-dependent, and temporary nature as physical illnesses only occur in some patients. Seventy-four case histories of patients who were treated at Grodno Regional Clinical Center “Psychiatry-narcology” in the period from 24 May 2016 to 24 June 2016 were analysed. In total their numbers were 64 men (23-69 years) and 10 women (23-53 years). 69% of the patients were diagnosed with the withdrawal syndrome due to alcohol consumption and the alcohol dependence syndrome (including 67% of males and 80% females). 31% of patients were diagnosed with the withdrawal syndrome, complicated with delirium (14.8%), convulsions (12.1%), and alcoholic hallucinosis (8%). In the primary biochemical analysis, indices of blood liver enzymes and bilirubin were elevated (AST - 70% of patients, ALT - 50%, total bilirubin - 19%). After treatment, the biochemical parameters reached normal levels. Chronic hepatitis was diagnosed in 5% of patients, who were all men.

The absence of alcoholic liver disease in the vast number of patients with chronic alcohol intoxication may be due to the following reasons: firstly - with undiagnosed somatic diseases. Secondly, the fact that the patients admitted to psychiatric hospital were with predominantly mental and behavioural disorders due to use of alcohol, while patients with alcoholic liver disease are more likely to receive medical care in somatic hospitals, where alcohol dependence often goes unrecognised. Official statistics of such "disguised" alcoholic pathology has not been carried out. Thirdly, associated with alcohol disease with symptoms of alcohol degradation and intellectual decline is not always accompanied. In such case, an external factor such as alcohol may be involved in the formation and becomes chronic of somatic diseases through epigenetic changes.

It is necessary to change the approach to the identification, treatment and prevention of alcohol dependence associated with somatic disorders and somatic diseases associated with alcohol intake.
COENZYME A SEQUESTRATION, GLUTATHIONE SYSTEM AND ALCOHOL METABOLIC ENZYMES DURING TREATMENT WITH VALPROIC ACID IN ALCOHOL INTOXICATION


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Ethanol and its metabolites can induce oxidative stress due to reactions with free thiol groups. Excessive amount of acetyl-CoA in acute alcohol intoxication can lead to metabolic acidosis and affect the free CoASH/acetyl-CoA ratio. Valproic acid has an anticonvulsant effect and it is metabolized by the liver, forming metabolites which can produce esters with CoASH. Utilization of CoA for energy metabolism and depletion of its pool due to sequestration result in metabolically less active valproyl-CoA which can subsequently increase the severity of liver damage and lead to accumulation of toxic intermediates including the central nervous system. The aim of this study was to examine the CoA and GSH status in the rat liver and brain after combined administration of ethanol and valproic acid and to evaluate the metabolic effects of D-panthenol which acts as a precursor in CoASH synthesis. The data obtained show that ethanol administration (10 g/kg) for 5 days significantly increased the levels of acid soluble brain CoA, free CoA and short-chain acyl-CoA compared to control values. Supplementary treatment with valproic acid (200 mg/kg) for 5 days significantly decreased free CoA and acyl-CoA levels in comparison with the control group. The administration of D-panthenol (400 mg/kg) in combination with ethanol and valproic acid was associated with reduction of acid-soluble COA to normal levels mostly due to the increased free CoA. Similar, but less pronounced, changes in CoA levels and its fractions were observed in rat liver tissues. The levels of total CoA and long-chain acyl-CoA were not changed, either in the liver, or in cerebral tissues. The combined administration of ethanol and valproic acid during alcohol intoxication resulted in significant disturbances in glutathione metabolism in the brain tissue but was less pronounced in the liver. In alcohol intoxication, D-panthenol was found to produce a neuroprotective effect while attenuating the disruption of the thiol status in brain tissue. Due to the metabolic disorders following alcohol intoxication the activity of rat liver alcohol metabolic enzymes remained essentially unaffected, except for the group of animals treated with D-panthenol where a significant increase in the activity of high Km ALDH and ADH was found. In contrast, the activity of high Km ALDH in the CNS was decreased in the valproic acid - treated group.
BRAIN HISTAMINERGIC NEURONS IN THE CONDITIONS OF SINGLE AND REPEATED EXPOSURE TO ALCOHOL

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The brain histaminergic system participates in the regulation of alcohol consumption and alcohol-related behavior. At the same time alcohol has significant influence on the brain histamine metabolism. The aim of the present paper was to analyze the histological, histochemical and ultrastructural changes of rat brain histaminergic neurons following acute (4 g/kg) and subacute (4 g/kg/day for 7 days) exposure to alcohol. This evaluation was carried out by the use of histological, histochemical, morphometric, cytophotometric and electron microscopy analysis methods.

Acute and subacute alcohol intoxication led to rounding of perikarya and nuclei of brain histaminergic neurons. After single ethanol administration, the average sizes of the cells were not significantly changed; under the influence of subacute alcohol intoxication the histaminergic neuron bodies became larger. This may be associated with a disturbance in the electrolyte balance and an alteration of the cytoskeleton of neurons, induced by ethanol. The single and repeated alcohol administration led to increase of monoamine oxidase type B, lactate dehydrogenase and acid phosphatase activities, which indicates acceleration of the processes of brain histamine oxidative deamination and additional activation of the late glycolysis stages under anaerobic conditions and intensifying of autophagy processes. Alcohol decreases glucose-6-phosphate dehydrogenase and NADPH-dehydrogenase activities, and this is indicative of weakening of extramitochondrial energy processes. The sevenfold ethanol administration depresses the activities of succinate dehydrogenase and NADH-dehydrogenase, which may reflect deceleration of the Krebs cycle and electrons transport in the mitochondrial respiratory chain. After the alcohol administration, increased size of nucleoli, shift of them to the nuclear border, aggregation of ribosomal subunits between nucleoli and nuclear envelope, extension of the perinuclear space and increased folding of nuclear envelope were observed. Hypertrophy of the Golgi complex, extension of the canals and cisterns of the endoplasmic reticulum, hypertrophy and hyperplasia of lysosomes occurred. There were found nucleoli-like bodies in histaminergic neurons following sevenfold exposure to alcohol. Some mitochondria were swollen with destructed crista and clear matrix. Thus, the histaminergic neurons following alcohol administration exhibited destructive processes and structural signs of hyperactivity, as well as intensive functioning related to their adaptation to alcohol.

In conclusion, the administration of ethanol produces a variety of histological, histochemical and ultrastructural changes in histaminergic neurons, some being common to all administration regimes and others being dependent on duration of exposure to alcohol. In parallel with the destruction processes in brain neurons following ethanol administration, repair and adaptation events took place in them. This may be a part of complex changes in brain following alcohol exposure.
ARGININE SUCCINATE AND ETHYL PYRUVATE HAVE HEPATOPROTECTIVE ACTION IN CHRONICALLY ALCOHOL-INTOXICATED RATS

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Earlier it was shown that ethyl pyruvate alleviates the severity of ethanol-induced oxidative stress and diminishes the extent of DNA damage in erythrocytes of alcohol-treated rats. Succinate treatment contributes to maintenance of mitochondrial energy-producing function under stress, hypoxia and intoxications. We found that arginine succinate shortened ethanol narcosis time and increased ethanol elimination rate. High doses of arginine could attenuate behavioral signs of alcohol abstinence. The aim of the work was to study a novel pharmaceutical substance, arginine succinate, synthesized at the Institute of Physico-Organic Chemistry, NAS of Belarus, as well as ethyl pyruvate as substances reducing chronic alcohol toxicity for the liver.

During the last 12 days of seven-week alcohol intoxication (5 g/kg, i/g) Wistar male rats were administered with physiological saline (ethanol group), ethyl pyruvate (100 mg/kg, i/g) and arginine succinate (400 mg/kg, i/g). Intact animals served as control for all the experimental groups. Rat liver samples were taken for histological examination. Paraffin sections were stained with hematoxylin and eosin and sudan black for detection of lipids.

Chronic alcohol intoxication during 5 weeks significantly increased the activity of alanine aminotransferase, concentrations of triglycerides and tumor necrosis factor alpha (TNF-α) in blood serum of rats to be indication of hepatotoxic and proinflammation action of ethanol. The administration of ethyl pyruvate during 2 weeks to alcohol intoxicated animals prevented a rise of triglycerides level in blood serum. The treatment with arginine succinate significantly decreased γ-glutamyltransferase activity and TNF-α content in serum compared to animals receiving ethanol without treatment. In the liver, chronic alcohol administration markedly decreased the activity of aldehyde dehydrogenase (ALDH) with low K_m – the main enzyme of acetaldehyde oxidation, and administration of ethyl pyruvate and arginine succinate normalized enzyme activity.

The histological examination revealed that under chronic alcohol intoxication leukocyte infiltration enhanced, increased the number of hyperchromic, polyploid nuclei, and microvesicular lipid dystrophy was found in the cytoplasm of hepatocytes. The use of both substances during alcohol intoxication had a corrective effect on liver morphology, which was more pronounced in arginine succinate.

Thus, our results demonstrate that arginine succinate and ethyl pyruvate have hepatoprotective properties.
ALCOHOL-RELATED PROBLEMS IN RUSSIA AND BELARUS: A COMPARATIVE ANALYSIS

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Alcohol is a major contributor to premature deaths toll in Eastern Europe. Its effects on mortality seem to have been especially striking in the Slavic countries of the former Soviet Union, where it has been identified as one of the most important factors underpinning the mortality crisis that has occurred in the post-Soviet period.

This study examines the trends in alcohol-related problems in Russia and Belarus from the late Soviet to post-Soviet period. It goes beyond previous studies that have been confined primarily to Russia and focused on alcohol-related mortality with few examples from elsewhere even though other former Soviet republics have experienced similar fluctuations in alcohol-related mortality rates. More specifically, this study focuses on a comparative analysis of trends in alcohol poisoning mortality rates, liver cirrhosis mortality rates, alcoholic psychoses incidence rates and alcohol sales per capita in Russia and Belarus.

Methods. The data on alcohol poisoning mortality rates, liver cirrhosis mortality rates, alcoholic psychoses incidence rates (per 100,000 of the population) and the data on per capita alcohol sales (in liters of pure alcohol) are taken from the Russian State Statistical Committee (Rosstat) reports and the Belarusian State Statistical Committee (Belsstat).

Results and Discussion. According to the results, in Russia, alcohol sales are statistically significant associated with all indicators of alcohol-related problems, implying that a 1-l increase in per capita alcohol sales is associated with the increase in the alcohol poisoning mortality rates of 9.0%, the increase in the liver cirrhosis mortality rates of 5.8% and the increase in the alcoholic psychoses incidence rates of 18.6%. In Belarus, alcohol sales are statistically significant associated with alcohol-related morbidity and mortality rates, implying that a 1-l increase in per capita alcohol sales is associated with the increase in alcohol poisoning mortality rates of 8.1%, and increase in the liver cirrhosis mortality rates of 5.5%, and the increase in the alcoholic psychoses incidence rate of 18.8%.

According to the results of the present analysis there was a positive and statistically significant effect of per capita alcohol sales on alcohol-related problems rates in Russia and Belarus and the magnitude of this effect was similar in both countries. These results are consistent with the previous findings that highlighted a close temporal association between alcohol-related morbidity and mortality rates and population drinking.

In conclusion, this comparative time-series analysis highlighted a close temporal association between the alcohol-related morbidity and mortality rates and the population drinking in Russia and Belarus. The outcomes of this study provide indirect support for the hypothesis that the dramatic fluctuations in the alcohol-related problems rates in Russia and Belarus during the last decades were related to the availability/affordability of alcohol. The findings from the present study have important implications as regards alcohol policy, suggesting that any attempts to reduce alcohol-related burden should be linked with efforts through restriction of availability/affordability of alcohol.
**ALCOHOL INTOXICATION AND THYMUS FREE AMINO ACIDS**

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Chronic alcohol consumption decreases the amount of CD4 + and CD8 + T lymphocytes in the thymus and spleen. Simultaneously, the level of soluble CD8 blood proteins, which can inhibit the activation of CD8 + T-lymphocytes, increases, which in its turn contributes to immunodeficiency. During the studies in chronic alcohol intoxication on animals a decrease of the mass of the thymus and spleen was recorded. Acetaldehyde is one of alcohol intoxication mediators, which interacts with proteins of immune cells, causing a disturbance of their function. In particular, acetaldehyde forms neoantigens which modify the immune response [1]. The synthesis and its regulation in cells are largely determined by the concentrations of regulatory and limiting amino acids.

The aim of the work was to study the influence of alcohol intoxication on the spectrum of free amino acids in the thymus tissue of rats.

The experiment was performed on 14 female albino rats, with the weight of 120-140 g. The ethanol (25% solution) was administered intragastrically. During the first 7 days of the experiment ethanol was administered at the dose of 7.5 g/kg, and subsequent 6 days - 5 g/kg. The rats were decapitated 24 hours after the last dose of ethanol. Determination of free amino acids in thymus tissue was carried out by reversed-phase HPLC.

After the course administration of ethanol, the thymus tissue showed decreased contents of asparagine (18.7%), threonine (18.2%) and isoleucine (12.7%). At the same time methionine catabolism inhibition was observed: the levels of cystathionine (52%) and taurine (11%) decreased. Probably as a result of modification of phospholipid metabolism by ethanol and its metabolites, the content of phosphoethanolamine (11.4%) decreased. The inhibition of protein synthesis in thymocytes could be due to the decrease of the total amount of essential amino acids (from 2393 ± 104 to 2091 ± 82 mmol/g), and amino acids with a branched carbon chain (leucine, isoleucine, valine) (from 1022 to 889 mmol/g), which resulted in the reduction of the nitrogen-containing amino acid metabolites (from 584 to 19 270 ± 17 323 ± 376 mmol/g). Depression of antioxidant status occurred as a result of the drop in sulfur amino acids levels (from 12074 to 10882 ± 356 ± 256 mmol/g).

It was demonstrated that intensive alcoholisation (daily at dose of 4.5 g/kg) during 3 days reduces the concentrations of asparagine (45%), phosphoethanolamine (49%), citrulline (36%) isoleucine (39%), valine (36%) and ethanolamine (30%). The intensive alcoholisation, like chronic intoxication, leads to a decrease in the total number of nitrogen-containing amino acid metabolites. In contrast to the course of the introduction of ethanol, short intensive alcoholisation in rats causes an increase of glutamate, histidine, alanine and ornithine levels.

Thus, the prolonged and intensive animal alcoholisation causes disturbance of the amino acid balance in the tissues of the thymus, which can indirectly indicate of its dysfunction, and in particular, of maturation and proliferation of T-lymphocytes, which leads to the distortion of the immune response.

CENTRAL EFFECTS OF BETULIN AND BETULIN DIACETATE DURING ETHANOL WITHDRAWAL IN RATS

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Pharmacological manipulation of GABA receptors may be one way to treat alcohol-related diseases and ethanol withdrawal. It has been shown recently that betulin acts as positive modulator of GABA(A) receptors. The lupane type terpenoids are widely distributed natural compounds, and among them betulin is most abundant. Effects of the lupane terpenoids on alcohol-related pathology have not been examined.

Purpose. The aim of the present study was to evaluate the effects of some lupane type triterpenoids on the severity of alcohol withdrawal in rats.

Methods. Male Wistar rats weighing 200–220 g were used in the experiments. Ethanol (30%, w/v) was administered intragastrically 2 times a day with a 12-h interval over 5 days at doses of 4–6 g/kg. After 13 h of alcohol cessation, rats were subdivided into 5 groups (n=10) which did not differ in severity of alcohol withdrawal signs. Alcohol withdrawal severity was assessed visually according to the ranged scale. Betulin and lupeol were isolated from birch bark. Betulin diacetate and betulinic acid were synthesized from betulin as described elsewhere. Terpenoids were emulsified in 2% w/v starch and administered intragastrically at 13 h 30 min after ethanol at doses of 100 mg/kg. Control animals received water. After 18 hours following ethanol withdrawal, the animals were sacrificed and their brains were removed and dissected. Amino acids were modified by pre-column derivatization with OPA+3-MPA and determined by RP-HPLC.

Results. After 13 hours following ethanol withdrawal, the animals had withdrawal signs whose severity increased, reached a peak after 15 hours and remained at approximately the same level for up to 17 hours in the ethanol-treated group. Betulin and betulin-3,28-diacetate but not lupeol or betulinic acid decreased on the average by 30-50% the severity of the ethanol withdrawal signs in rats after 15-17 hours. After 18 hours following ethanol withdrawal, amino acid levels in different brain areas (frontal cortex, basal ganglia, cerebellum, and hippocampus) showed a significant imbalance between excitatory and inhibitory amino acids. Betulin and betulin diacetate normalized the levels of some neuroactive amino acids, especially GABA. We suggest that most of these effects are caused by affinity of triterpenes to GABA(A) receptors. The observation that lupeol and betulinic acid did not show any effect against alcohol withdrawal is in good agreement with the earlier published data that they are chemically closely related to betulin, but are not bound to GABA(A) receptors.

Conclusion. The results obtained show the ability of betulin and betulin-3,28-diacetate to decrease the severity of ethanol withdrawal in rats and to normalize the levels of some neurotransmitter amino acids in different brain areas. This fact raises the possibility that these compounds might possess some therapeutic benefits in alcohol-use disorders.
ALCOHOL USE AMONG HIGHER SCHOOL STUDENTS: MULTICENTER STUDY

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Introduction. Alcohol consumption in Belarus and in neighboring countries is still high. The most vulnerable social group in terms of possible alcoholisation is higher school students. Control over alcohol consumption among higher school students is very complicated because of widespread and high alcohol consumption in the population.

Purpose. The main purpose of this study was to obtain information about transboundary characteristics of alcohol use and alcohol consumption control among higher school students on both sides of the eastern border of the European Union.

Methods. A self-completion questionnaire based on a PAV-10 and LimeSurvey web application as an online front-end was used for surveying of higher school students. Respondents were volunteers and subjects recruited from university and further education college populations in 5 countries (Russia, Belarus, Poland, Lithuania and Ukraine). The purpose of the survey and clear assurances that all questionnaires would be completed anonymously was explained to respondents. The survey was conducted using a sample of 4135 higher school students aged 16 to 25 years (1159 males and 2976 females). The STATISTICA software was used to store, code, clean, and analyze the data, using t-tests, and chi-square tests for categorical data.

Results. A comparative study of alcohol consumption in 8 control cities found that the most popular alcoholic beverages among higher school students were beer (88.3% of consumers) and strong drinks (8.6%). Wine and champagne were rarely called "youth alcoholic beverages". Almost two-thirds of the respondents consumed alcohol in the past 30 days, and 41.8% more than once. These persons preferred beer (33.0%), vodka, cognac and other strong drinks - 24.8%. Alcohol intake the day before they were surveyed was indicated by 11.8% of the students. Only 6.2% of the respondents strongly denied alcohol drinking. Almost 12% of the students did not consider alcohol intake something reprehensible. Only a third of the respondents condemns or rather condemns alcohol intake by peers. There are significant differences in the responses received, depending on the country where the survey was conducted.

Conclusion. Weakening control over alcohol consumption in Poland and Lithuania universities highlights risky alcohol behavior of students in these countries against their peers from Russia, Ukraine and Belarus. Almost all students drink alcohol and often do not find reasons for refusal of alcohol consumption. Alcoholic beverages are recognized by respondents as an attractive tool for communication of young people, which involves it use for free pastime.
FREE AMINO ACIDS IN BLOOD PLASMA OF RATS UNDERGOING ALCOHOL EXPOSURE IN DIFFERENT MODES

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It is a well-known that liver, pancreas, heart and brain are the main targets of toxic effects of ethanol. Free amino acids (AAs) imbalance following alcohol intoxication plays an important role in the pathogenesis of chronic alcohol intoxication and withdrawal and arises mainly from insufficient intake of dietary AAs, impairment of their absorption and function of the liver. Study of the AA imbalance patterns in various experimental situations may amend the approaches to its correction. Our main goals were to estimate the characteristics and to conduct a comparative analysis of the AA pool structure in blood plasma of rats undergoing various modes of alcohol exposure as well as its withdrawal.

Methods. All experiments were carried out on male albino rats of heterogeneous stock. Chronic ethanol intoxication (ChAI) was simulated by substituting the drinking water with ethanol solution (20%) during 14 weeks. Subchronic ethanol intoxication (SAI) was modeled by intragastric administration twice a day of 25% ethanol solution in a daily dose of 28 ml/kg during 28 days. Ethanol withdrawal was modeled according to Majchrowicz. Amino acids analysis was carried out by reversed-phase HPLC with pre-column derivatization with o-phthalaldehyde and detection by fluorescence.

Results. Ethanol withdrawal was accompanied with raised levels of taurine, alanine, methionine and histidine in blood plasma. A rise of the glycosogenous and ketogenous AAs ratio has been also observed. The statistical analysis of free AAs pool components demonstrated a significant contribution of the above-listed taurine, alanine, and methionine levels as well as the levels of glutamate and phenylalanine to discrimination of control and abstinent groups. Three-month ChAI resulted in decreased blood plasma levels of glycine, methionine, histidine and increased concentration of tyrosine. The ratio of the total branched-chain AAs (BCAA) levels to aromatic amino acids (AAA) levels was reduced by ChAI, while the total amount of proteinogenic AAs and the ratio of nonessential / essential AAs remained unchanged. The most significant components characterizing AAs imbalance were tyrosine, threonine and glycine. In the group of animals undergoing SAI, the blood plasma levels of alanine, proline, tryptophan and beta-alanine were elevated, along with the decreased levels of alpha-aminoburate. In this case, the level of tyrosine remained unchanged. SAI was also accompanied with an elevated ratio of nonessential / essential AAs and the ratio of glycosogenous and ketogenic AAs.

The comparative analysis of ChAI and SAI provide evidence for distinctions of its effects on the BCAA and AAA levels in blood plasma. This must be taken into account when using hepatoprotective drugs based on BCAA administration of such preparations at the early stages of alcoholization may be unfavorable due to competitive blocking of the AAA transport in brain.
PANTOTHENIC ACID METABOLISM IN THE ORGANISM OF WHITE RATS UNDER CHRONIC ALCOHOL INTOXICATION

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The pantothenic acid metabolism has been sufficiently studied. In the literature, there is evidence of disturbed CoA formation in tissues of animals with chronic alcohol intoxication. However, the problem of CoA catabolism, especially that of pantothenic acid under alcohol poisoning, has not been investigated so thoroughly.

Our investigation was carried out on mongrel white rats weighting 180-220 grams. For one month the animals were administered by gavage with 1 ml of 40% ethanol and thereafter they were used in the experiment. All procedures with animals were carried out according to the rules of the Guide for the Care and Use of Laboratory Animals. We determined pantothenic acid and its metabolites in animal organs by column chromatography on DEAE-cellulose.

As a result, our research showed that in the animals receiving 40% ethyl alcohol for a month, the CoA content was decreased in the majority of tissues. This phenomenon was manifested especially markedly in the animal liver and brain. The changes in the level of pantothenic acid under alcohol intoxication were significant. At the same time the level of pantothenic acid catabolites, β-alanine and pantoic acid in the liver, and, particularly in the brain, were significantly increased.

Thus, our research shows that chronic alcohol intoxication leads to disruption of CoA biosynthesis and stimulates disintegration of pantothenic acid.
THE EFFECTS OF FOLINIC ACID ON HEPATIC CYTOCHROME P450 ENZYMES IN ETHANOL-FED RATS

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Cytochrome P450 (P450) enzymes are important in the metabolism of drugs, chemicals and endogenous substrates. Alterations in hepatic P450s function can change the pharmacokinetics and efficacy of drugs, as well as affect the metabolic processes that they mediate. P450s are induced by many of their substrates, including ethanol.

We studied the effects of folinic acid (5-formyl-5,6,7,8-tetrahydrofolate) on the hepatic P450s content and activities in ethanol-fed rats. Animal experiments were performed in accordance with the international principles on the Care and Use of Laboratory Animals. Male Wistar rats (130–150 g) were fed the Lieber-DeCarli liquid diet containing ethanol (36% of energy) or isocaloric carbohydrates as control diet for 6 weeks. The ethanol group was subdivided into two groups; one of the groups was treated with 17.5 mg/kg/day (i.p.) of folinic acid, and another group and the control group were injected with saline solution (3 ml/kg/day). P450s content and metabolic activities were evaluated in rat liver microsomes which were prepared by differential centrifugation.

Chronic ethanol feeding significantly increased the total hepatic P450s content (by 43%) and catalytic activity of the individual P450 isoforms: P4501A1-mediated ethoxyresorufin O-dealkylation, P4501A2-mediated methoxyresorufin O-dealkylation, P4502B1/2-mediated pentoxyresorufin O-dealkylation, P4502E1-mediated p-hydroxylation of aniline (by 39%, 84%, 83%, 113%, respectively). Folinic acid caused a marked loss of ethanol-induced hepatic P4501A2, 2B1/2 and 2E1 activities in rats. Thus, the O-dealkylations of methoxy- and pentoxyresorufin were decreased by 52% and 48%, respectively, and p-hydroxylation of aniline – by 23%. Furthermore, the total P450s content and P4501A1 activity of ethanol-fed rats given folinic acid were unchanged compared to controls.

The results showed that folinic acid reduces the inducing effect of ethanol on the hepatic P450s enzymes in chronic ethanol-fed rats.
Natural Grape Products Against Alcoholism

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The threatening growth of alcoholism in the world results in increased death rates which follow after such causes as cardiovascular, oncological diseases and injuries. The etiology, pathogenesis, diagnosis and treatment of alcoholism-associated diseases remain topical problem. The development of alcoholism is associated with consumption of strong alcoholic beverages and their surrogates. The high levels of acetaldehyde and NADH are produced as a result of oxidation of exogenous ethanol. These changes lead to oxidative stress development and other metabolic disturbances in almost all organs and systems. At the same time, acetaldehyde is the one of the major regulatory factors of energy metabolism and psychosomatic status. The deficiency of endogenous acetaldehyde as well as its storage form ethanol is one of the causes of some forms of pathology and the formation of alcohol addiction. Therefore, it is necessary to keep concentration of mentioned above metabolites within the physiological range.

For cases when alcohol consumption could not be excluded for some reasons it should be recommended to use natural grape wines. This idea as alternative mean of overcoming alcoholism was proposed more than a hundred years ago by the outstanding scientist V. Tairov who was a founder of the Russian station wine-growers and winemakers. Evaluating the idea from the standpoint of modern science, we note that it remains relevant today for some reasons. As a rule, the moderate concentration of ethanol in wines does not disturb acetaldehyde dependent metabolic processes. The organic wine components activate and improve the efficiency of detoxification systems via mimicking the pattern of normal anaerobic metabolites. Slight oxidative stress together with a huge variety of other polyphenols and other compounds with antioxidant activity stimulate protective mechanisms, increasing resistance to various forms of pathology. Besides, reasonable wine consumption gives a person a true delight due to slight sedative effect on the cortex and brain structure regulating autonomic functions. Thus, the mentioned above beverage could demonstrate a lot of helpful effects in case of moderate consumption.

Recent studies show that alcohol-free wines could provide healthy beverage without toxic effects and conserving all salutary effects. Hence mild gradual decreasing in alcohol content could be effective strategy of alcoholism prevention with keeping of socio-cultural background, familial traditions and personal habits. The Institute has selected new high polyphenol-containing grapes suitable for manufacturing of high quality products with a high level of bioactive substances.
METABOLISM OF THIAMINE IN WHITE RATS UNDER CHRONIC ALCOHOL INTOXICATION

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The problem of vitamin anabolism under chronic alcohol intoxication has not been sufficiently investigated. In the literature, there is evidence of violations of vitamins content and their transformation into biologically active forms. At the same time the question of changes in the catabolism of vitamins in the body under alcohol intoxication still remains almost unexplored. Our studies were performed on mongrel white rats weighting 180-220 g. The animals were administered with 1 ml of 40% ethanol via gavage, daily, for one month. All procedures with animals were carried out according to the rules of the Guide for the Care and Use of Laboratory Animals.

Thiamine metabolites were determined in organ homogenates via ascending paper chromatography. The studies showed that the compound of thiamine and its coenzyme form, thiamine pyrophosphate, was significantly reduced in the majority of the investigated organs. The most intensive decrease was observed in the liver and brain.

The level of free thiamine in rats treated with alcohol during the month declined not so significantly as that of TPP. The level of the main thiamine catabolites, blood thiochrome and 4-methyl-5β-oxyethyl-thiazole, increased by 20-40%. Thiochrome elevation was observed only in the liver, whereas increase of 4-methyl-5β-oxyethyl-thiazole was noticed in the brain. Thus, our results indicated that the chronic use of alcohol for a month reduced the thiamine phosphorylation to TPP and increased the formation of its catabolism. These effects are organ-specific.
L-ARGININE METABOLISM UNDER ALCOHOL INTOXICATION: OXIDATIVE AND NON-OXIDATIVE PATHWAYS

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Ethanol and its oxidated intermediates can influence the level of redox processes in the cell with involvement of NO-dependent signaling and metabolic pathways. Nitric oxide synthases (NOS) catalyze the production of nitric oxide (NO) converting $O_2$ and L-arginine to NO and L-citrulline at the physiological level. Additionally the production of NO in cells is regulated by arginase. This enzyme competes with NOS for their substrate, L-arginine, and converts it to urea and ornithine. Under pathological conditions, the balance between oxidative and non-oxidative pathways may vary.

The aim of the present study was to investigate the effect of L-arginine (NOS substrate) and L-NAME, Nω-nitro-L-arginine methyl ester (non-specific inhibitor of NOS), on the balance between oxidative and non-oxidative pathways of L-arginine metabolism under alcohol intoxication. A rat model of alcohol intoxication (AI) was used as previously described (Yefimenko, 2015).

It was revealed that the value of NOS total activity in erythrocytes of rats with AI decreased by 65% compared to the control group. After L-arginine administration, the total NOS activity increased in both groups. Furthermore, after L-arginine consumption, in the control group of animals the enzyme activity increased 1.2-fold in the control animal group, whereas in the group of animals with AI it elevated 1.9-fold. The consumption of the non-selective NOS inhibitor, L-NAME, which is a structural analog of L-arginine, was accompanied by 23.4% decreased total NOS activity in controls and by 25% diminished one in the pathologic state. A change in iNOS activity comparable to the total NOS activity was observed. In the control group of animals, iNOS activity amounted to 27.3% of the total activity. After L-arginine administration to the control group of animals, iNOS activity amounted to 16.4% of the total enzyme activity. This index is 1.7-fold less than in the control, whereas after L-NAME intake by the control group the enzyme activity amounted to 39.4% of the total activity, which is 1.4-fold higher compared to the control. In animals with AI, this index amounted to 44.5% of the total enzyme activity, after the intake of L-NAME this index was slightly decreased (21.1%), whereas the intake of L-arginine promoted the return of iNOS activity to the control levels.

It was found that arginase activity increased in red blood cells of peripheral blood in alcohol-intoxicated rats. It was confirmed by 2.3-fold higher concentration of urea in comparison with the control group. After L-arginine consumption, control animals showed increased urea amount in hemolysates of rat blood, but it was decreased in the group with AI. After L-NAME consumption, the urea concentration was not changed in both groups. We found that L-arginine metabolism by oxidative pathway is inhibited under AI.
STUDY OF THE PROTECTIVE EFFECT OF THIAMINE AND ITS METABOLITES IN ACUTE INHALATORY ALCOHOL INTOXICATION

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The problem of alcohol intoxication via inhalation has been insufficiently studied. At the same time workers at companies producing alcoholic beverages are constantly suffering from this intoxication. Therefore, the aim of our study was to investigate a possible protective effect of thiamine and its metabolites intoxication by ethanol vapor.

The investigations were carried out on mongrel white rats weighting 180-220 grams. Control animals were parenterally injected by saline, whereas experimental animals were administered with thiamine and its metabolites at a dose of 1 µm per kg. The animals were placed in sealed cameras, which were continuously fed with air- saturated ethanol vapor. All procedures with animals were carried out according to the rules of the Guide for the Care and Use of Laboratory Animals. After 2, 4, 8, 24 and 48 hours the activities of pyruvate dehydrogenase and alcohol dehydrogenase in animal tissues were detected. In other experiments, the survival rate was studied in control animals and after an injection of thiamine individual metabolite.

The studies showed that thiamine and, especially, thiochrome increased the survival of the animals, under the action of ethyl alcohol, compared to control in which the animals were not injected with thiamine and its metabolites. A decrease of alcohol dehydrogenase and pyruvate dehydrogenase activity in the liver and small intestine after an injection of thiochrome alone was observed. The level of ethanol in the blood was also significantly decreased. Pyruvate dehydrogenase activity in the liver and small intestine was increased after the TPP injection. Thus, our study confirmed earlier investigations in our laboratory showing multi-directional action of the thiamine coenzyme form and its catabolites on the ethanol metabolism in the body.
APPLICATION OF CYCLODEXTRIN NANOCONSTRUCTIONS FOR THE TREATMENT OF ALCOHOLIC LIVER DISEASE

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Cyclodextrins (CD) are cyclic carbohydrates which are of nanosize and could form inclusion complexes with poor water-soluble organic compounds. The complexation of CD with sparingly soluble drugs increased their solubility, as well as bioavailability and specificity of treatment. Recently we demonstrated that the nanocomplexation with the CD derivative, 2-hydroxypropyl-β-CD (HPβCD), increased the solubility and pharmacological effect of sertraline, selective inhibitor of serotonin reuptake, which is widely used as antidepressant in diabetic patients for improvement of depression and glycemic control. The treatment of diabetic animals with HPβCD: sertraline complex reduced the severity of diabetes, as evidenced by lowering of blood glucose and glycated hemoglobin contents, increasing of insulin level and improving pancreatic islet morphology and β-cell survival. These effects of the complex were more pronounced as compared to the antidiabetic action of both the monopreparations, HPβCD and sertraline. Among new medicines developed for prevention and treatment of alcoholic liver disease and other liver pathologies over the past decades much attention has been drawn to plant-derived polyphenols. Herbal compounds are multi-targeted and have less toxic side effects, but are poorly water-soluble, which causes their low bioavailability. Recently we have complexed cranberry extracts and betulin with HPβCD to improve its pharmacological properties. The hepatoprotective effect of nanocomplexes in rats with alcoholic steatohepatitis in comparison with monopreparations was significantly higher, suggesting availability of this approach in the treatment of alcoholic liver disease.
Prenatal alcohol exposure affects brain cortex neurons postnatal development in rats

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Alcohol consumption during pregnancy induces specific disorders in offspring that are combined under the term Fetal Alcohol Syndrome (FAS), which is a part of the Fetal Alcohol Spectrum Disorders (FASD). It is well known that a developing nervous system, especially brain cortex, is particularly sensitive to alcohol exposure. The purpose of the present study was estimation of the effect of prenatal alcohol exposure on the histological, histochemical, immunohistochemical and ultrastructural characteristics of neurons in the frontal cortex of rats at different time periods after birth. Rats of experimental groups received a 15% solution of ethanol as a single source of drinking throughout the whole pregnancy, and the animals of the control group – equivolume amount of water. The average consumption of alcohol was 4.64±2.2 g/kg/day. The brains of the offspring of the control and alcohol groups were collected on the 2nd, 5th, 10th, 20th, 45th and 90th days after birth for further histological, histochemical and electron microscopy analysis. Statistical evaluation after normality test was carried out using nonparametrical methods, the morphometrical differences were considered significant at p<0.05. It was found that the antenatal alcohol exposure in rats increased (on the 2nd and 5th postnatal days), and then reduced (on the 10th and 90th days) the brain cortex thickness, and a decrease in the relative amount of brain cortex neurons and an increase in the number of their pathological forms were observed throughout all the time periods of the examination. Starting from the 20th postnatal day shrinkage and cessation of the growth of brain cortex neurons were observed. We found a significant reduction in the number of mitochondria per μm² of the cytoplasm and the total length of its cristae, an increase in the free ribosomes number, reduction of the rough endoplasmic reticulum canal length and a comparative amount of bound ribosomes, expansion of the Golgi complex cisternae, as well as an increase of the lysosome number and size in the cytoplasm of neurons. The histochemical examination revealed inhibition of NADH-and succinate dehydrogenases (marker enzymes of mitochondria), NADPH, glucose-6-phosphate dehydrogenase and activation of lactate dehydrogenase and acid phosphatase (marker enzymes of lysosome). The immunohistochemical investigation demonstrated disturbances in synaptogenesis and maturation of neurons in the frontal cortex after prenatal alcoholisation. In conclusion, alcohol consumption during pregnancy in rats induces deep and irreversible structural and metabolic changes of the cerebral cortex neurons and various, severe and long-term behavioral and mental disorders in the offspring.
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2-й Симпозиум Восток-Запад по биомедицинскому изучению алкоголязависимых заболеваний. Программа и материалы симпозиума