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Effect of vitamin B3/niacin complex with germanium (VI) on the content of fatty acids in the brain, liver and kidneys of alcohol-exposed rats

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ABSTRACT

Chronic ethanol consumption increases the production of reactive oxygen species, which damage cell structures, leading to pathological changes in the body, including fatty acid metabolism disorders. Vitamin B3 has antioxidant and protective properties and improves the body's condition in case of toxic lesions of various geneses, and its complexes with metals may have additional protective effects. The aim of this study is to investigate the effect of the complex compound of nicotinic acid with germanium (Ge) (IV) on the composition of fatty acids (FA) in brain, liver and kidney tissues in rats with forced alcoholisation, which was modelled by administering 20% ethanol as the only source of liquid for 110 days. The qualitative composition and quantitative content of FAs in tissues was studied by gas chromatography and expressed as a percentage of the total FA content, in the spectrum of which 5 unsaturated (myristic, pentodecanoic, palmitic, margaric, stearic acids) and 4 saturated FAs (oleic, linoleic, linolenic, arachidonic acids) were identified. Long-term use of 20% ethanol caused organ-specific changes in the lipid spectrum of the studied animal tissues. In alcohol-exposed rats, the level of polyunsaturated arachidonic acid decreased by 78% in the brain, by 22% in the liver, and by 68% in the kidneys. A decrease in palmitic acid content was also observed in the nervous tissue, but this did not affect the ratio of saturated to unsaturated FAs. Administration of the complex normalised the content of palmitic and arachidonic acid in the nervous tissue and the level of polyunsaturated fatty acids; in the liver of rats, the content of polyunsaturated FAs increased by 15% and its precursor linoleic acid by 73%; in the kidneys, the ratio of saturated to unsaturated FAs increased. Further elucidation of the mechanisms of action of the complex compound of niacin with germanium under conditions of alcohol consumption opens up the prospects of studying it as a drug to prevent the prooxidant activity of ethanol.

KEYWORDS: germanium-nicotinate complex, fatty acid, ethanol, antioxidant.

1. INTRODUCTION

According to the WHO, alcohol abuse is one of the biggest risks of developing a group of non-communicable diseases [1]. It is known that chronic ethanol consumption increases the production of reactive oxygen species [2], which damage the structure of lipids, proteins and DNA of cells and cellular homeostasis in general [3-5] and lead to a number of pathological changes in the body, including disorders of fatty acid (FA) metabolism in various organs [6-10].

Saturated fatty acids (SFAs) serve as an energy substrate [11, 12], while unsaturated fatty acids (UFAs) are structural components of phospholipids

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in biological membranes and ensure the functioning of membrane proteins and transport of substances across cell membranes [13]. Polyunsaturated fatty acids (PUFAs) in the phospholipids of cell membranes are the main substrate for lipid peroxidation (LPO) [14]; therefore an increase in reactive oxygen species (ROS) levels leads to modification of protein-lipid contacts and changes in cell membrane permeability [15]. PUFAs are involved in the regulation of gene expression [16, 17] and the mitochondrial stage of apoptosis [18, 19]. In addition, PUFAs serve as a precursor of eicosanoids - inflammatory mediators that regulate immune responses [20-24]. Among others, liver, brain and kidney cells are sensitive to the toxic effects of ethanol and its active metabolite acetaldehyde [25].

There is evidence that niacin has antioxidant properties [26, 27], improves alcohol-induced liver damage [28] and may exert neuroprotective effects through interaction with the GPR109A receptor [29]. In addition, the complex compound of niacin and germanium has shown neuroprotective activity in chronic alcoholism [30], cytoprotective activity in chronic doxorubicin intoxication [31, 32] and may be promising in the development of intoxication of various geneses [33]. Other niacin complexes with metals have shown the ability to mimic superoxide dismutase activity [34], and a copper complex with nicotinic acid has shown nephroprotective activity in glycerol toxicity [35] and non-alcoholic fatty liver disease [36].

The aim of this study is to investigate the effect of vitamin B3/nicotinic acid complex with Ge (IV) on the composition of fatty acid lipids in brain, liver and kidney tissues in rats with forced alcoholisation.

2. MATERIALS AND METHODS

The work was performed on female Wistar rats (mean weight 197.7 ± 3.1 g), which were kept in the vivarium of Bogomolets National Medical University (Kyiv, Ukraine) in accordance with the requirements of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Purposes [37] and in agreement with the Bioethics Commission. Animals were selected based on the results of a two-bottle ethanol choice test [38]. The animals were divided into 3 groups: Group 1 - intact animals (n = 6), Group 2 - a model of forced alcoholism - rats receiving 20% ethanol as the only source of fluid for 110 days (n = 6), Group 3 - animals with forced alcoholism, which from day 90 were intraperitoneally injected with a solution of the complex compound of nicotinic acid with germanium (MIGU-1, synthesised at the Odesa National University named after I. I. Mechnikov (Odesa, Ukraine) at a dose of 10 mg/kg/day (n = 6). Animals were euthanised on day 111 after the start of the study under thiopental anaesthesia (20 mg/kg), followed by extirpation of the brain, liver and kidneys. The qualitative composition and quantitative content of FAs in tissues were studied by gas chromatography [39].

Statistical analysis was performed using Statistica 10.0 (StatSoft, Inc., USA) using the Mann-Whitney U test. Data are presented as arithmetic mean (M) and standard deviation (±SD). Differences between groups were considered significant at $P<0.05$.

3. RESULTS AND DISCUSSION

In the chromatographic study of the fatty acid composition of lipids in the brain, liver and kidneys, the values were obtained as a percentage (%) of the total fatty acid content. 5 UFAs (myristic acid $C_{14:0}$, pentodecanoic acid $C_{15:0}$, palmitic acid $C_{16:0}$, margaric acid $C_{17:0}$, stearic acid $C_{18:0}$) and 4 SFAs (oleic acid $C_{18:1}$, linoleic acid $C_{18:2}$, linolenic acid $C_{18:3}$, arachidonic acid $C_{20:4}$) were identified in the spectrum of fatty acids. It has been previously described that the main effect of ethanol and acetaldehyde is seen in their ability to depress the function of the central nervous system, causing a wide range of neurological and mental disorders [40-42]. Chronic alcohol consumption leads to increased levels of ROS and LPO in neurons, which leads to DNA damage, inhibition of gene expression and neuronal death [43-45]. With prolonged ethanol use in the brain tissue (Table 1) of rats of group 2, a decrease in palmitic acid content by 13% and an increase in stearic and oleic acids by 25% and 15%, respectively, were observed compared to group 1 ($P<0.05$). Such changes in the brain of

Table 1. Content of higher fatty acids in the nervous tissue of rats under conditions of chronic alcoholism and the influence of MIGU-1.

Name of FA	Code of FA	Nervous tissue		
		1st group	2nd group	3rd group
Myristic	$C_{14:0}$	0.4 ± 0.1	0.4 ± 0.1	0.6 ± 0.1
Pentodecanoic	$C_{15:0}$	-	0.4 ± 0.1	0.6 ± 0.1
Palmitic	$C_{16:0}$	37.4 ± 1.3	32.6 ± 1.5*	36.4 ± 1.0#
Margaric	$C_{17:0}$	-	0.4 ± 0.1	0.6 ± 0.1
Stearic	$C_{18:0}$	15.4 ± 1.0	19.3 ± 1.0*	20.1 ± 1.0*
Oleic	$C_{18:1}$	38.0 ± 1.0	43.7 ± 1.5*	32.3 ± 1.5*,#
Linoleic	$C_{18:2}$	0.8 ± 0.1	0.9 ± 0.3	1.1 ± 0.1*
Linolenic	$C_{18:3}$	-	0.4 ± 0.1	0.6 ± 0.1
Arachidonic	$C_{20:4}$	7.8 ± 0.5	1.7 ± 0.3*	7.7 ± 0.5#
∑ SFA		53.2 ± 1.5	53.1 ± 1.5	58.3 ± 1.2*,#
∑ UFA		46.8 ± 1.5	46.9 ± 1.5	41.7 ± 1.2*,#
∑ PUFA		8.6 ± 1.0	3.0 ± 1.0*	9.4 ± 0.5#

*P<0.05 compared to the 1st group (intact group).
#P<0.05 compared to the 2nd group.

rats of group 2 did not affect the SFA-to-UFA ratio compared to intact animals. However, the amount of PUFAs decreased by 65% due to a 78% decrease in the content of arachidonic acid compared to group 1 (P<0.05), which may indicate activation of lipid oxidation in the brain tissue under conditions of chronic ethanol consumption, which is consistent with the literature [46]. Significant changes in the content of stearic acid, which, on one hand, is synthesised from palmitic acid, and, on the other hand, acts as a substrate for the synthesis of monounsaturated oleic acid, can be considered as an adaptation and compensatory mechanism aimed at maintaining the balance of SFAs and UFAs at the physiological level.

The administration of nicotinic acid with germanium normalised the content of palmitic and arachidonic fatty acids and the level of PUFAs in the nervous tissue. The content of stearic acid did not change compared to group 2 and remained high compared to group 1. There was a decrease in the content of oleic fatty acid by 26% compared to group 2, by 15% compared to group 1 (P<0.05) and an increase in the content of linoleic acid by 38% compared to group 1 (P<0.05). It was found that in the nervous tissue of rats of the 3rd group the content of the fraction of UFAs decreased by 11% compared to the 1st and 2nd groups (P<0.05).

Ethanol ingestion is completely metabolised in the liver by the two enzymes alcohol dehydrogenase and aldehyde dehydrogenase [47], making this organ particularly susceptible to acetaldehyde damage. During chronic alcohol consumption, changes in the redox state of hepatocytes caused by LPO process contribute to the development of alcoholic liver disease [9]. With prolonged ethanol consumption, changes in the content of fatty acid lipids in the rat liver differed from changes in the composition of brain tissue fatty acids (Table 2). In the liver tissue of rats of group 2, a 37% decrease in the content of stearic fatty acids and a 12% increase in the content of palmitic fatty acids were found compared to group 1 (P<0.05) (Table 2).

Table 2. Content of higher fatty acids in the liver of rats under conditions of chronic alcoholism and the influence of MIGU-1.

Name of FA	Code of FA	Liver		
		1st group	2nd group	3rd group
Myristic	$C_{14:0}$	0.4 ± 0.1	0.5 ± 0.1	0.6 ± 0.1
Pentodecanoic	$C_{15:0}$	-	0.5 ± 0.1	0.6 ± 0.1
Palmitic	$C_{16:0}$	31.6 ± 1.5	35.5 ± 1.5*	20.6 ± 1.0*,#
Margaric	$C_{17:0}$	-	0.5 ± 0.1	0.6 ± 0.1
Stearic	$C_{18:0}$	18.0 ± 1.0	11.3 ± 1.0*	14.0 ± 0.8*,#
Oleic	$C_{18:1}$	17.9 ± 1.0	26.1 ± 1.0*	30.6 ± 1.5*,#
Linoleic	$C_{18:2}$	8.5 ± 0.5	6.3 ± 0.5*	10.9 ± 1.0*,#
Linolenic	$C_{18:3}$	-	0.5 ± 0.1	0.6 ± 0.1
Arachidonic	$C_{20:4}$	23.7 ± 1.0	18.6 ± 0.5*	21.4 ± 1.0#
∑ SFA		50.0 ± 1.5	48.3 ± 1.3	36.4 ± 1.1*,#
∑ UFA		50.0 ± 1.5	51.7 ± 1.3	63.6 ± 1.1*,#
∑ PUFA		32.2 ± 1.3	25.4 ± 1.0*	32.9 ± 1.0#

*P<0.05 compared to the 1st group (intact group).
#P<0.05 compared to the 2nd group.

It is possible that the detected change in the content of SFAs in the liver tissue is facilitated by the conversion of ethanol to acetic acid. The formation of reduced NADH in the process of ethanol metabolism causes an increase in the ratio of NADH/NAD+, which contributes to the inhibition of β-oxidation of fatty acids in the liver [6]. An increase in oleic acid by 46%, a decrease in arachidonic acid by 22% and its precursor linoleic acid by 26% were found in the spectrum of liver UFAs of rats of group 2 compared to group 1 (P<0.05). These changes did not significantly affect the ratio of SFA to UFA in the liver of group 2 rats compared to intact animals. However, in the liver of group 2 rats, as well as in the brain, we observed a decrease in the amount of PUFAs, but only by 21% compared to group 1 (P<0.05). It is likely that in the liver of rats of group 2, a cascade of lipid peroxidation reactions was triggered due to oxidative stress caused by the toxic effect of alcohol on hepatocytes. Lipid oxidation leads to damage to the membrane of subcellular structures, such as the endoplasmic reticulum, Golgi complex, mitochondria and lysosomes, disruption of intracellular homeostasis and induction of cell survival mechanisms under stress [48, 49].

It was found that under the influence of nicotinic acid with germanium in the liver lipids of rats of the 3rd group, the content of palmitic acid decreased by 42% and the amount of stearic acid increased by 24% compared to the 2nd group (P<0.05). However, despite such changes, the level of palmitic and stearic acids in the liver of animals of group 3 was lower compared to group 1 (P<0.05), and the content of oleic acid increased by 17% compared to group 2 and by 71% compared to group 1. Presumably, such a change in the fatty acid content is associated with the fact that monounsaturated oleic acid, which is synthesised from stearic acid, is an essential fatty acid for the formation of structural components (glycerolipids and cholesterol esters) of the very low density lipoproteins [50]. The introduction of

the complex against the background of chronic alcohol consumption normalised the content of PUFAs in the liver of rats of group 3 due to an increase in the content of arachidonic acid by 15% and its precursor linoleic acid by 73% compared to group 2 ($P<0.05$). In the liver of animals of group 3, the content of linoleic acid increased by 28% compared to group 1 ($P<0.05$), and the ratio of the content of SFA to UFA significantly decreased. The amount of SFA in the liver of animals of group 3 decreased by 27% compared to group 1 ($P<0.05$), which can be considered as a positive liver fatty lipid pool, since an excess of SFA can provoke the development of fatty liver, cirrhosis or liver failure [51].

The kidneys play an equally important role in the body's detoxification process. In addition, the kidneys are involved in regulating water and salt balance, maintaining blood pressure and eliminating metabolic end products. After drinking alcohol, ethanol and its metabolites pass through the kidneys and are excreted in the urine. Numerous studies have shown that chronic alcohol consumption disrupts the concentration, reabsorption and secretory functions of the kidneys due to the activation of the LPO process by ethanol and changes in the structure of renal tubular membrane lipids. The vulnerability of the kidneys to oxidative damage is partly explained by the high content of long-chain polyunsaturated fatty acids in kidney tissue. The contents of fatty acids in the kidneys of animals of the 2nd group shown in Table 3 show that under conditions of chronic ethanol consumption, the level of palmitic acid increases by 23% and stearic acid decreases by 17% compared to the 1st group ($P<0.05$). It should be noted that similar changes were observed in the liver of rats of group 2, while in the brain the nature of the changes was the opposite. An increase in the ratio of SFA to UFA content in the kidneys of group 2 rats was recorded compared to intact animals. A decrease in the content of PUFAs was observed in all studied tissues. Thus, in the kidneys of rats of

Table 3. Content of higher fatty acids in the kidney of rats under conditions of chronic alcoholism and the influence of MIGU-1.

Name of FA	Code of FA	Kidney		
		1st group	2nd group	3rd group
Myristic	$C_{14:0}$	0.8 ± 0.1	0.6 ± 0.1	0.4 ± 0.1
Pentodecanoic	$C_{15:0}$	-	0.6 ± 0.1	0.4 ± 0.1
Palmitic	$C_{16:0}$	34.8 ± 1.5	42.9 ± 1.3*	38.8 ± 1.5*,#
Margaric	$C_{17:0}$	-	0.6 ± 0.1	0.4 ± 0.1
Stearic	$C_{18:0}$	16.2 ± 1.0	13.5 ± 1.0*	14.4 ± 1.0
Oleic	$C_{18:1}$	32.6 ± 1.3	34.4 ± 1.3	26.8 ± 1.0*,#
Linoleic	$C_{18:2}$	8.6 ± 0.5	4.5 ± 0.5*	5.7 ± 0.6*,#
Linolenic	$C_{18:3}$	-	0.6 ± 0.1	0.4 ± 0.1
Arachidonic	$C_{20:4}$	7.2 ± 0.3	2.3 ± 0.3*	12.6 ± 1.0*,#
∑ SFA		51.8 ± 1.6	58.2 ± 1.0*	54.4 ± 1.5#
∑ UFA		48.2 ± 1.6	41.8 ± 1.0*	45.5 ± 1.5#
∑ PUFA		15.8 ± 1.5	7.4 ± 0.8*	18.7 ± 1.0#

*$P<0.05$ compared to the 1st group (intact group).
#$P<0.05$ compared to the 2nd group.

group 2, the amount of PUFAs decreased by 53% due to the influence of linoleic and arachidonic acids, compared to group 1 ($P<0.05$), which may indicate the activation of lipid peroxidation in the renal tissue under the influence of ethanol.

After administration of the complex compound of nicotinic acid with germanium against the background of chronic ethanol consumption in the kidneys of rats of group 3, the content of palmitic acid decreased by 10% compared to group 2 ($P<0.05$), but was 12% higher in comparison with group 1 ($P<0.05$). There were no significant changes in the content of stearic acid in the kidneys of rats of group 3 compared to groups 1 and 2, and the content of oleic acid decreased by 18% compared to group 1 and by 22% compared to group 2 ($P<0.05$). The introduction of the complex compound of nicotinic acid with germanium contributed to the restoration of the amounts of SFA and UFA compared to the 2nd group. An increase in the content of linoleic acid and its metabolic product arachidonic acid in the kidneys of rats of group 3 was observed by 27% and 5.47 times, respectively, compared to group 2 ($P<0.05$). At the same time, while the level of linoleic acid was 34% lower, the level of arachidonic acid was 75% higher compared to group 1 ($P<0.05$). These changes were reflected in the amount of PUFAs, which increased by 2.52 times compared to group 2 ($P<0.05$) and did not differ significantly from group 1. It is assumed that the normalisation of the SFA/UFA/PUFA ratio of the lipid complex of the kidneys of alcohol-addicted rats after administration of the studied complex may indicate a slowing down of oxidative stress and a stoppage of cell damage caused by the toxic effect of ethanol and its metabolic products at the molecular level.

In summary, it was found that long-term consumption of 20% ethanol by rats caused organ-specific changes in the distribution of FAs in the lipid spectrum of the studied tissues (brain, liver, kidney), which is associated with different qualitative and quantitative lipid content and peculiarities of lipid metabolism in different organs. It is important to note that in the nervous tissue, unlike liver and kidneys, the level of palmitic acid decreased under the influence of ethanol. As recently reported in the literature, palmitic acid not only serves as an energy substrate, but also participates in the post-translational modification of proteins, which is known as palmitoylation. Palmitoylation modification is important for the maintenance of intracellular homeostasis and cell survival under oxidative stress. Disturbance of the balance between palmitoylation and depalmitoylation affects glioma cell viability, apoptosis, invasion, self-renewal and pyroptosis [52, 53]. The direct effect of ethanol on lipid metabolism in the brain, liver and kidneys activates the oxidation of unsaturated fatty acids while inhibiting β-oxidation of fatty acids [6]. Administration of the MIGU-1 against the background of long-term ethanol consumption inhibited lipid peroxidation processes caused by ethanol.

4. CONCLUSION

The complex of vitamin B3/nicotinic acid with germanium had a beneficial effect on the spectrum of brain, liver and kidney lipids in alcohol-exposed rats, in which long-term consumption of 20% ethanol reduced the amount of PUFAs in the nervous tissue, liver and kidneys, indicating a possible activation of the lipid peroxidation process under the influence of ethanol. The administration of the complex compound restored the content of FAs depending on the changes induced by ethanol, namely: palmitic acid in nervous tissue, arachidonic acid in nervous tissue and liver, stearic acid in kidneys, the sum of PUFAs in nervous tissue, liver and kidneys and the ratio of SFAs/UFAs in the kidneys of rats. Further elucidation of the mechanisms of action of the nicotinic acid-germanium complex under conditions of alcohol consumption opens up the prospects of studying it as a drug to prevent the prooxidant activity of ethanol.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest regarding the publication of this article.

ABBREVIATIONS

FA : fatty acids
LPO : lipid peroxidation
MIGU-1 : complex compound of nicotinic acid with germanium

PUFA : polyunsaturated fatty acids
ROS : reactive oxygen species
SFA : saturated fatty acids
UFA : unsaturated fatty acids

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