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Role of hydrogen sulphide in biochemical mechanisms of myocardial damage in alcoholic cardiomyopathy

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Abstract. Excessive alcohol consumption, which is observed in many patients, causes cardiovascular diseases, in particular alcoholic cardiomyopathy, but the role of changes in H_2S metabolism in heart damage in this pathology remains understudied. Therefore, the study aimed to determine the role of hydrogen sulphide in the mechanism of heart damage in alcoholic myocardial injury in rats. The study was carried out on 35 white male Wistar rats weighing 260-290 g, divided into two groups. The study determined that the development of alcoholic cardiomyopathy in rats is accompanied by the development of pathobiochemical processes, including cardiomyocyte apoptosis, inflammation, development of oxidative and nitrosative stress, as evidenced by a significant increase in the content of caspase-3 (5.23 times) of tumour necrosis factor α (70.2%), malondialdehyde of carbonyl groups of proteins (2.7 and 2.5 times), respectively, as well as imbalance in the system of nitric oxide synthases (increase in inducible and decrease in endothelial isoform (+94.4 and -40.0%, respectively, $p < 0.05$). All these changes were associated with a decrease in myocardial hydrogen sulphide content (-36.0%, $p < 0.05$). The correlation and permutation analysis confirmed the relationship between the content of hydrogen sulphide and markers of cardiac damage in alcoholic cardiomyopathy, namely, a low content of the gas transmitter was associated with more severe disorders, while a higher level of hydrogen sulphide, on the contrary, was associated with moderate or minimal signs of cardiac damage under conditions of chronic alcoholism in animals. Assessment of the level of hydrogen sulphide in the body can predict the development of alcohol-induced heart damage and is an experimental basis for the development of H_2S-releasing drugs to improve the pharmacological management of patients

Keywords: alcoholic myocardial injury; hydrogen sulphide; inflammation; apoptosis; oxidative stress; NO synthase; rats

INTRODUCTION

Excessive alcohol consumption is observed in a wide range of patients worldwide. The World Health Organization (WHO) defines alcohol as toxic, psychoactive and addictive [1]. Alcohol consumption remains the third most important risk factor for poor health worldwide; excessive alcohol consumption is one of the four most common modifiable risk factors for major non-communicable diseases [2]. In Ukraine, according to a WHO sociological survey conducted in 2023, 77.4% of the adult population consumed alcohol during the year (80.1% and 75.2% of men and women, respectively), and in 2021, the average per capita consumption of pure alcohol per year in Ukraine was 8.1 litres [3]. Although the number of people who reduced alcohol consumption exceeded the number of those who increased it since the outbreak of full-scale war, this problem remains severe, as it usually causes health and social problems, Alcohol consumption is responsible for 3 million annual deaths worldwide in addition to disability

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and related diseases affecting millions of people, with a global burden of disease estimated at 5.1% (7.1% for men and 2.2% for women) [1]. Alcohol is the main risk factor for premature mortality and disability among people aged 15-49 years, accounting for 10% of all deaths in this age group; in the 20-39 age group, ~13.5% of all deaths are alcohol related.

Among the targets of the negative impact of chronic alcohol consumption, the cardiovascular system is distinguishable, since alcoholic cardiomyopathy (ACM), which is a progressive cardiac dysfunction, dilated cardiomyopathy, causes heart failure and other heart diseases, often with fatal consequences. M. Shahid *et al.* [4] analysed mortality rates in the United States for 1999-2020 and estimated the Social Vulnerability Index (SVI), which determined the impact of a range of external stressors on the infrastructure and community well-being. The study demonstrated that the SVI index is directly correlated with alcohol abuse and mortality from ACM. The literature describes the negative changes that occur in the myocardium under conditions of direct and indirect toxic effects of alcohol in a thorough manner. However, according to C. Andersson *et al.* [5], some issues remain insufficiently studied due to the lack of systematic population-based studies and a small number of described clinical cases. The data on the reversibility of negative morphological changes in the heart after alcohol abstinence also appear controversial. There is no definitive evidence of sex differences in the development of this pathology, although some results indicate that, despite the generally higher number of men who abuse alcohol, alcohol-induced heart damage occurs more rapidly in women.

The pathobiochemical mechanisms of ACM development and progression are also far from being fully elucidated, which significantly hinders the effective prevention and treatment of this pathology. The protective role of H_2S in the treatment of ischemia-reperfusion injuries of various organs (heart, brain, liver, intestines, lungs, spinal cord, etc.) was described by X. Sun *et al.* [6], which became the basis for testing H_2S-releasing molecules in the treatment of these conditions. F.M. Payne *et al.* [7] demonstrated that hydrogen sulphide, along with two other gas molecules – nitrogen monoxide (NO) and carbon monoxide (CO), provide anti-inflammatory effects on the myocardium in experimental myocardial infarction due to inhibition of the proinflammatory inflammasome NLRP3, which reduces the regulation of cellular inflammation as a pathobiochemical link in myocardial damage. Clinical confirmation of the protective effect of the donor hydrogen sulphide – sodium thiosulfate in patients with myocardial infarction was also obtained by M.L. de Koning *et al.* [8]. The pleiotropic effects of H_2S (antioxidant, vasodilator, antiapoptotic, anti-inflammatory, etc.) are correlated with the pathogenesis of other myocardial lesions, such as diabetic cardiomyopathy, as demonstrated by S. Zhao *et al.* [9]. To date, there is no literature data on changes in H_2S metabolism and their role in heart damage in alcoholic cardiomyopathy. The study aimed to determine the role of hydrogen sulphide in the mechanisms of heart damage in alcoholic myocardial damage in rats.

MATERIALS AND METHODS

During the experimental studies, the standards of current legislation and international guidelines for conducting medical and biological research using animals were maintained [10]. The experiment included male Wistar rats weighing 260-290 g of mature age, kept in the vivarium of the National Pirogov Memorial Medical University, Vinnytsya (the room temperature was maintained in the range of 20-22°C, and the relative humidity was within 50 ± 5%) and maintained on a standard diet. The experiments were conducted with consideration of daily and seasonal rhythms, and all manipulations were performed under standard conditions from 9:00 to 10:00. Following the aim and objectives of the study, all experimental animals were divided into 2 groups. Animals in the experimental group (20 rats) were modelled for 90 days with alcoholic cardiomyopathy by intragastric administration of a 20% aqueous ethanol solution (8 g/kg/day) [11]. Animals in the control group (15 rats) were administered freshly boiled water in equivalent volumes. A 20% ethanol solution and water were administered daily. After 90 days, the animals were euthanised by dislocation of the cervical vertebrae, and then the hearts were removed for further studies. The rat hearts were perfused with 1.15% potassium chloride solution and then homogenised in 1.15% potassium chloride (1:3 ratio) at 3,000 rpm. The resulting homogenate was centrifuged for 30 min at 600 g and aliquots of the supernatant were taken into Eppendorf microtubes. The H_2S content in the heart was determined by the method of B. Wiliński *et al.* [12]. The levels of the apoptosis marker caspase-3 and the proinflammatory cytokine TNF-α in the rat heart were determined by enzyme-linked immunosorbent assays using the corresponding kits "Rat Caspase-3 ELISA Kit" (Elabscience Biotechnology Inc., USA) and "Rat TNF-α ELISA Kit" (Elabscience Biotechnology Inc., USA) on a STAT-FAX 303+ analyser (USA).

The protein level in the postnuclear supernatant of the heart was determined by the spectrophotometric method according to the Lowry method [13], the content of malondialdehyde (MDA) was estimated in the reaction of formation of a coloured complex with 2-thiobarbituric acid [14], and the carbonyl groups of proteins (CG) – in the reaction of hydrazone formation with the participation of 2,4-dinitrophenylhydrazine [15]. The total NO synthase activity, as well as the activity of its isoforms (endothelial and inducible), was determined by spectrophotometric methods by increasing the amount of nitrite anion after incubation in the corresponding incubation mixtures, as described by N. Hula *et al.* [16].

Statistical processing of the primary material was performed using Statistica 18.0 (StatSoft Inc., USA). The results were presented as M ± m. To assess the probability of differences in indicators, parametric and nonparametric criteria (Student and Mann-Whitney U) were used. The relationship between the indicators was determined by Pearson and Spearman correlation analysis. The critical level of significance was assumed to be 5%.

RESULTS AND DISCUSSION

The data obtained in this study demonstrated that chronic alcoholisation of experimental animals caused significant changes in biochemical parameters of heart function. Thus, the content of hydrogen sulphide in the myocardial homogenate of rats of the experimental group was statistically significantly reduced (by 36.02 %) compared to that of control animals (Table 1). At the same time, signs of

apoptosis and inflammation were recorded, as evidenced by a significant increase in the corresponding markers – caspase-3 (5.23 times) and TNF-α (70.2 %) compared to animals without experimental pathology.

Table 1. Influence of alcoholic cardiomyopathy on the content of hydrogen sulphide, apoptosis and inflammation in the rat heart (M ± m)

Biochemical parameters of the heart	Control, n = 15	Alcohol cardiomyopathy, n = 20
H_2S, nmol/mg protein	3.22 ± 0.13	2.06 ± 0.08*
Caspase-3, ng/mg protein	0.237 ± 0.020	1.24 ± 0.04*
TNF-α, pg/mg protein	161 ± 5.69	274 ± 6.17*

Notes: * – p < 0.05 compared to the control group of animals
Source: compiled by the authors

These disorders were also accompanied by other signs of myocardial damage by alcohol and its derivatives, such as the development of oxidative and nitrosative stress and endothelial dysfunction. The data presented in Table 2 show that alcoholic cardiomyopathy is accompanied by an imbalance in redox balance with a significant increase in prooxidant processes. This is evidenced by a significant increase in the content of markers of oxidative stress (products of fat and protein peroxidation) – malondialdehyde and carbonyl groups of proteins (2.7 and 2.5 times, respectively (p < 0.05).

The results demonstrated that prolonged alcohol use is accompanied by an imbalance in the vasodilator/vasoconstrictor system towards the predominance of vasoconstrictor molecules, which is accompanied by dysfunction in the NO synthase system – decreased expression of the endothelial NOS isoform and decreased sensitivity of blood vessels to the vasodilating effect of NO and increased expression of the inducible NOS isoform, which causes the development of nitrosative stress, since under these experimental conditions the content of endothelial NO synthase decreased by 40.0% and inducible NO synthase increased by 94.4%, respectively, compared to the animals without experimental pathology (p < 0.05).

The permutation and correlation analyses performed provided evidence of the involvement of hydrogen sulphide in the development of ACM (Table 3). Thus, under conditions of experimental pathology, the content of H_2S in the heart had a positive correlation of a high degree with the content of endothelial NO synthase (r = 0.84, p < 0.05), and in group 3, where the level of hydrogen sulphide was the highest, the level of this vasodilator was 117.6% higher than in group 1, where the H_2S content was the lowest.

Table 2. Influence of alcoholic cardiomyopathy on endothelial dysfunction, nitrosative and oxidative stress in rat heart (M ± m)

Biochemical parameters of the heart	Control, n = 15	Alcohol cardiomyopathy, n = 20
eNOS, pmol/min·mg protein	5.40 ± 0.30	3.24 ± 0.23*
iNOS, pmol/min·mg protein	1.79 ± 0.13	3.48 ± 0.20*
MDA, μmol/mg protein	2.54 ± 0.21	6.86 ± 0.28*
CG, nmol/mg protein	0.710 ± 0.020	1.78 ± 0.03*

Notes: * – p < 0.05 compared to the control group of animals
Source: compiled by the authors

Table 3. Permutation and correlation analysis between biochemical parameters of rat heart damage and hydrogen sulphide level in alcoholic cardiomyopathy

Biochemical parameters of the heart	H_2S, nmol/mg protein			
	r	$<P_{25}$ 1.66 ± 0.06	P_{25}-P_{75} 2.01 ± 0.04	$>P_{75}$ 2.55 ± 0.06
		Group 1	Group 2	Group 3
Caspase-3, ng/mg protein	-0.65&	1.41 ± 0.06	1.24 ± 0.04*	1.07 ± 0.04*#
TNF-α, pg/mg protein	-0.58&	307 ± 5.84	271 ± 6.50*	248 ± 6.83*#
eNOS, pmol/min·mg protein	+0.84&	2.04 ± 0.19	3.24 ± 0.23*	4.44 ± 0.20*#
iNOS, pmol/min·mg protein	-0.78&	4.54 ± 0.18	3.45 ± 0.22*	2.48 ± 0.10*#
MDA, μmol/mg protein	-0.70&	8.31 ± 0.27	6.87 ± 0.26*	5.38 ± 0.24*#
CG, nmol/mg protein	-0.72&	1.91 ± 0.02	1.79 ± 0.03*	1.63 ± 0.03*#

Notes: * – p < 0.05 relative to the corresponding indicators corresponding to the level of hydrogen sulphide in the percentile interval up to P25; # – p < 0.05 relative to the indicators corresponding to the level of hydrogen sulphide in the percentile interval P_{25}-P_{75}; & – reliability (p < 0.05) of the correlation coefficient (r)
Source: compiled by the authors

Negative correlations of medium strength were established between the content of hydrogen sulphide in the heart and indicators of myocardial damage – levels of caspase-3, TNF-α, MDA, CGP, and inducible NO synthase ($r = -0.65, -0.58, -0.70, -0.72$, and -0.78, respectively ($p < 0.05$). The permutation analysis demonstrated that in group 1, where the myocardium of animals had the lowest content of hydrogen sulphide, the elevation of these parameters was the most pronounced and was significantly 24.1, 19.2, 35.2, 14.7 and 45.4% higher than the changes in the corresponding parameters in the myocardium of animals with the highest H_2S content. The obtained results confirm the relationship between the level of hydrogen sulphide and pathobiochemical parameters of heart damage in alcohol-induced heart injury and provide the basis for further research in this area to identify the H_2S system as a target for drug effects.

The diagnosis of ACM can be made in the presence of the following features: heavy alcohol consumption (>80 g/day) for 5 years or more, left ventricular end-diastolic diameter 2 times higher than normal, and a decrease in left ventricular ejection fraction <50% [17]. The incidence of ACM is gradually increasing as a result of widespread alcohol abuse, rendering ACM the leading cause of heart failure and sudden cardiac death in clinical practice [1-3].

The development of ACM is caused by a combination of direct toxic effects of alcohol on the myocardium, oxidative stress, mitochondrial dysfunction, and genetic predisposition. According to S. Wang & J. Ren [18], ethanol and its most toxic derivative acetaldehyde contribute to oxidative stress in the myocardium by promoting the formation of reactive oxygen species (ROS) or activating additional systems, such as the renin-angiotensin system. Experiments demonstrated that acute alcohol consumption in animals leads to mitochondrial dysfunction, impaired myocardial contractility and a decrease in overall peripheral vascular resistance. Thus, J. Tao *et al.* [19] showed that activation of phosphoglycerate mutase 5 (Pgam5) induced by AChP exacerbates alcohol-induced disorders in male mice by inducing dephosphorylation of prohibitin-2 and impairing mitochondrial quality control. Chronic alcohol consumption is toxic to cardiac myocytes, causing cell death, fibrosis and impaired contractility in both animal and human experimental models [20]. In addition, the effect of ethanol on NOX2 activation and subsequent oxidation of Ca/calmodulin-dependent kinase II (CaMKII) has been described, leading to Ca^{2+} release from the sarcoplasmic reticulum, which is one of the reasons for its arrhythmogenic and negative inotropic effects [21]. According to T.A. Manolis *et al.* [22], the arrhythmogenic potential of alcohol consumption leading to cardiac arrhythmia includes the induction of both atrial and ventricular arrhythmias, with atrial fibrillation (AF) being the most common alcohol-related arrhythmia, even with low/moderate alcohol consumption.

The results demonstrated that alcoholic cardiomyopathy in rats is accompanied by the development of such pathobiochemical processes as oxidative stress (increase in prooxidant molecules – MDA and CG), nitrosative stress (imbalance in the system of nitric oxide synthases: increase of inducible and decrease of endothelial isoforms), inflammation and apoptosis of cardiomyocytes (increase of caspase-3 and TNF-α in myocardium), $p < 0.05$). The data obtained are fully comparable with the results of other studies describing pathobiochemical changes in the myocardium under conditions of prolonged alcohol administration [5]. During the onset and development of ACM, various pathological changes in the myocardium may occur, accompanied by inflammation, apoptosis and other types of cell death, oxidative and nitrosative stress, and fibrosis. These changes are often asymptomatic at the initial stages and are detected at the stage of irreversible changes or after the occurrence of fatal complications. Treatment of these lesions is mainly symptomatic, which does not always lead to satisfactory results.

Therefore, the need for in-depth studies of pathobiochemical changes in ACMP and the identification of targeted approaches to modulate this pathology is quite apparent. From this perspective, hydrogen sulphide (H_2S), recognised as the third most common endogenous gaseous signalling molecule in mammals (along with NO and CO), has proven to be an important biochemical marker. The distinct cardioprotective effect of hydrogen sulphide and its donors was established by I. Palamarchuk *et al.* [23] on a model of diabetic cardiomyopathy, S.C. Kang *et al.* [24] in myocardial fibrosis, and A. Melnyk *et al.* [25] in post-perfusion cardiac lesions. These results also correlate with the data of N. Li *et al.* [26], according to which endogenous H_2S, possessing powerful vasodilatory properties, reduces ischaemic damage to the heart muscle induced by experimental myocardial infarction in mice. Along with the known mechanisms of positive organotropic effects of H_2S (the ability to eliminate mitochondrial and endothelial dysfunction, reduce oxidative and nitrosative stress, antiapoptotic properties, etc. Y. Zhang *et al.* [27] showed the ability of hydrogen sulphide to regulate the processes of pyroptosis (a type of cell death that leads to damage to cell membranes with the subsequent release of proinflammatory cytokines, including IL-1β and IL-18).

Despite the recognised organ-protective role of hydrogen sulphide in many diseases, the involvement of this gas transmitter during ACM and the mechanisms of this effect have been described in only a few publications. In particular, B. Liang *et al.* [28] demonstrated that preconditioning of the body with a hydrogen sulphide donor – NaHS significantly reduces fibrotic changes in the myocardium of mice with experimental ACM by reducing the expression of genes that cause autophagy and collagen 1.

The study demonstrated that the H_2S content in the heart was statistically reduced in the case of alcoholic myocardial damage, and this reduction correlated with the degree of negative changes in the myocardium. The data from the permutation analysis provided additional evidence that low levels of hydrogen sulphide in the myocardium indicate more severe pathological changes in the heart in ACM, while high levels of this gas transmitter, on the contrary, protect the heart from alcohol damage. This suggests that an increase in the content of hydrogen sulphide in the body (including using H_2S-releasing drugs or other drugs that increase the level of this gas transmitter) will contribute to more effective cardioprotection in the setting of ACM.

This hypothesis is supported by the results presented in the scientific literature. Thus, B. Tánczos *et al.* [29] demonstrated that an H_2S-releasing water-soluble ascorbic

acid derivative improved the function of the isolated cardiomyocytes under ischaemia-reperfusion conditions by providing a potent antioxidant effect, enhanced autophagy, and reduced apoptosis. The study by Q. Zhang *et al.* [30] on animals with myocardial ischaemia or inflammatory injuries determined that H_2S reduces ischaemic injury and suppresses inflammatory reactions in the myocardium by increasing the expression of microRNA-21. Thus, H_2S can reduce the intensity of fibrotic changes in the myocardium in ACM by regulating the levels of microRNA expression and cellular autophagy.

CONCLUSIONS

Alcoholic cardiomyopathy in rats is accompanied by the development of numerous pathobiochemical disorders in the myocardium, including the induction of cardiomyocyte apoptosis and inflammation, processes of free radical oxidation of lipids and oxidative modification of proteins, as evidenced by a significant increase in the content of caspase-3 (5.23 times), TNF-α (70.2%), MDA (2.7 times) and CG (2.5 times) in the myocardium compared to animals of the control group. Along with this, an imbalance in the NOS system was observed, accompanied by the development of nitrosative stress and endothelial dysfunction, as evidenced by a statistically significant increase in the activity of the inducible NOS isoform in the myocardium by 94.4% against a decrease in the activity of its endothelial isoform by 40.0% compared to the control group. The development of molecular and pathophysiological disorders in the heart against the background of prolonged alcoholisation is associated with a statistically significant decrease in the myocardial content of the gas-transmitter molecule H_2S by 36.0% compared with the control group.

The correlation and permutation analyses provided important evidence of the involvement of the H_2S system in the molecular mechanisms of alcoholic myocardial damage in rats. The study determined that low levels of the gas transmitter under conditions of chronic alcoholisation were associated with more pronounced pathobiochemical disorders in the heart (apoptosis, inflammation, oxidative-nitrosative stress, endothelial dysfunction), while at higher levels of H_2S, the intensity of these biochemical disorders was significantly lower. This creates a prospect for further research aimed at clarifying the mechanisms of H_2S action and developing new therapeutic approaches aimed at correcting the dysfunctions associated with ACM. H_2S is considered a promising molecular target for pharmacotherapy of alcoholic cardiomyopathy.

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CONFLICT OF INTEREST

None.

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Роль гідроген сульфіду в біохімічних механізмах ураження міокарду за алкогольної кардіоміопатії

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Анотація. Надмірне споживання алкоголю, яке спостерігається у багатьох пацієнтів, призводить до серцево-судинних захворювань, зокрема алкогольної кардіоміопатії, однак роль змін обміну H_2S в ураженні серця за цієї патології залишається недостатньо вивченою. Тому метою роботи було визначення ролі сірководню в механізмі пошкодження серця при алкогольному ураженні міокарда у щурів. Дослідження було проведено на 35 білих статевозрілих щурах-самцях лінії Wistar масою 260-290 г, поділених на дві групи. Встановлено, що розвиток алкогольної кардіоміопатії у щурів супроводжується розвитком патобіохімічних процесів, які включають апоптоз кардіоміоцитів, запалення, розвиток оксидативного та нітрозативного стресу, про свідчать вірогідне зростання вмісту в міокарді каспази-3 (в 5,23 рази) фактору некрозу пухлин α (70,2 %), малонового діальдегіду карбонільних груп протеїнів (2,7 та 2,5 рази), відповідно, а також розбалансуванням в системі синтаз оксиду азоту (підвищенням індуцибельної та зменшенням ендотеліальної ізоформи (+94,4 та -40,0 %, відповідно, $p < 0,05$). Всі ці зміни асоціювались із зниженням вмісту в міокарді гідроген сульфіду (-36,0 %, $p < 0,05$). Проведений кореляційний та персентильний аналіз підтвердив зв'язок між вмістом гідроген сульфіду та маркерами ураження серця за алкогольної кардіоміопатії, а саме – низький вміст газотрансміттера асоціювався із більш виразними порушеннями, тоді як більш високий рівень гідроген сульфіду – навпаки, асоціювався із помірними або мінімальними ознаками кардіальних уражень за умов хронічної алкоголізації тварин. Врахування рівня гідроген сульфіду в організмі дасть змогу прогнозувати розвиток алкоголь-індукованих уражень серця та є експериментальним підґрунтям для розробки H_2S-вивільняючих препаратів з метою покращення фармакологічного менеджменту пацієнтів

Ключові слова: алкогольне ураження міокарда; сірководень; запалення; апоптоз; оксидативний стрес; NO-синтаза; щури