UDC 616.127-018.18-615.099:547.262:546.289+547-327 doi: https://doi.org/10.15407/ubj97.01.051

BIOMARKERS OF APOPTOSIS AND ENDOPLASMIC RETICULUM STRESS IN CARDIOMYOCYTES OF RATS UNDER CHRONIC ETHANOL CONSUMPTION AND GERMANIUM-NICOTINIC ACID COMPLEX ADMINISTRATION

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Received: 11 November 2024; **Revised:** 03 February 2025; **Accepted:** 21 February 2025

Chronic ethanol consumption is associated with a range of harmful effects on different systems of the body, including the heart. Coordination complexes of bioactive compounds based on non-toxic metals are attracting interest in biomedical research due to their potential therapeutic properties. The study aimed to evaluate the influence of the germanium-nicotinic acid complex (MIGU-1) on apoptosis and endoplasmic reticulum (ER) stress indicators in the myocardium of rats under chronic alcohol exposure. Female Wistar rats were divided into three groups of 6 animals each: intact animals; rats that received 20% ethanol as the sole source of liquid for 110 days; animals with chronic consumption of 20% ethanol, which from the 90th day until the end of the experiment were intraperitoneally administered MIGU-1 solution (10 mg/kg/day). Biomarkers related to apoptosis, ER stress autophagy were assessed by Western blot analysis. It was shown that chronic ethanol consumption significantly activated apoptotic pathways in rat myocardium tissue, evidenced by increased levels of cleaved caspase-3 and BAX proteins alongside Beclin-1 level elevation, indicating enhanced autophagy. A significant decrease in the content of the protein IRE1 and its phosphorylated form in myocardial with no changes in GRP78 protein level was detected. Treatment with MIGU-1 resulted in both ethanol-induced apoptosis reduction and ER stress attenuation in cardiomyocytes with the level of Beclin-1 and GRP78 proteins remaining unchanged. Our findings demonstrate that the MIGU-1 complex promotes cardiomyocyte survival by balancing apoptosis and unfolded protein response, thus preventing alcohol-related cardiac injury.

K e y w o r d s: nicotinic acid, germanium, MIGU-1, alcohol intoxication, rat cardiomyocytes, apoptosis, ER stress, autophagy.

In recent years, the scientific literature has widely debated the impact of controlled alcohol consumption (ethanol) on the human body. Despite several epidemiological studies indicating that alcohol consumption in small or moderate amounts reduces the risk of major adverse cardiovascular events (MACE), there is still insufficient scientific evidence to explain this phenomenon conclusively [1, 2]. The vast majority of studies on the effects of alcohol on the human body have shown that acetaldehyde and other compounds formed during the biotransformation of ethanol in the human body lead to the activation of reactive oxygen species, oxidative stress, and disruptions in proteostasis [3]. This results in changes in the metabolism of cardiac muscle cells, damage to cardiomyocytes, and their death. The ethanol intake correlates with a decrease in the synthesis of ribosomal proteins, particularly actin, myosin, troponin, and titin, impairing the contractile ability of cardiac muscle. Moreover, acetaldehyde can interact with cellular proteins and form protein adducts, disrupting the structure and/or function of these proteins [4, 5].

The mechanisms by which alcohol and its metabolites influence the intricate system of intracellular signal transduction are still insufficiently

studied. Future research aimed at uncovering the internal mechanisms regulating cell death may enhance our understanding of the contradictory data regarding the effects of alcohol on the cardiovascular system [6]. It should be noted that excessive alcohol consumption causes numerous pathological stress reactions, one of which is the endoplasmic reticulum (ER) stress response. The specified pathogenetic mechanism leads to unfolded/misfolded protein accumulating in the ER lumen, contributing to alcohol-related disorders of major organs such as the liver, pancreas, heart, and brain [7]. This could also identify new drug targets for delaying or preventing diseases caused by chronic alcohol consumption.

Considering their low toxicity to the organism, germanium nano- and coordinative compounds have been shown to exhibit significant residual tumor elimination, sterilization, and potential wound-healing effects, also making them promising candidates for pharmacological treatment of cardiovascular, immune and neurodegenerative diseases [8-10]. One of the critical factors in accelerated cell death and ER stress is considered to be the depletion of the intracellular pool of NAD^+, the coenzyme form of vitamin B_3 (nicotinic acid) [11, 12]. Given the above and the great research interest in complex compounds of vitamins (especially group B) with metals [13-15], our focus was established on the protective effects of the germanium complex with nicotinic acid (MIGU-1) in alcohol intoxication. The aim of this study was to evaluate the potential therapeutic effects of the coordination compound germanium with nicotinic acid (MIGU-1) in the regulation of ER stress and apoptosis in cardiomyocytes of rats with chronic ethanol consumption.

Materials and Methods

The animals were kept in the vivarium of the Bogomolets National Medical University (Kyiv, Ukraine) with compliance with bioethical norms when conducting experimental research on animals, which was confirmed by the Commission on Bioethical Expertise and Ethics of Scientific Research of Bogomolets National Medical University (protocol No. 177 dated 23.10.2023). All animal procedures were performed in compliance with the requirements of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 1986).

The study was conducted on female Wistar rats (average weight 197.7 ± 3.1 g and 10 weeks old at the beginning of the experiment). The animals were selected based on the results of a two-bottle alcohol choice test [16], and they were divided into three groups: Group 1 – intact animals *(n* = 6), Group 2 – a model of chronic alcohol exposure - rats received 20% ethanol as the sole source of liquid, equivalent to ~9.0–10 g/kg/day, for 110 days (*n* = 6), Group 3 – the experimental group, animals with chronic consumption of 20% ethanol, which from the 90th day until the end of the experiment were intraperitoneally administered a solution of MIGU-1 (10 mg/kg/day) (*n* = 6) according to [17]. Note that groups 2 and 3 were consuming ethanol until the end of the experiment.

The research studied the regulatory properties of the coordination complex of germanium with nicotinic acid (laboratory code MIGU-1), synthesized for the first time in the laboratory of the department of inorganic chemistry and chemical education of the Odessa I. I. Mechnikov National University. This complex was characterized by IR and NMR spectroscopy, which allowed its structural chemical formula to be deciphered (Fig. 1). MIGU-1 synthesis was carried out by a uniform method. Weighed portions of ligands were dissolved in 10 ml of acetic acid, acetonitrile or tetrahydrofuran and $GeCl_4$ was added in molar ratios of metal:ligand = 1:4. The resulting precipitates were filtered using a vacuum manifold, washed with appropriate solvents and diethyl ether, dried to constant weight at ~100°C for 3 h [18].

The rats were sacrificed on day 110 after the beginning of the experiment using thiopental anesthesia (20 mg/kg). The heart was immediately removed, resuspended with saline buffer, and the myocardium

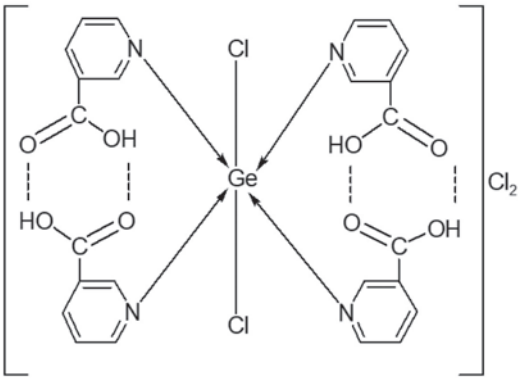

Fig. 1. Chemical structure of the germanium-nicotinic acid coordination complex (MIGU-1)

tissue was homogenized in the presence of liquid nitrogen until a homogeneous state was achieved. Myocardial proteins were extracted using RIPA (lysis) buffer with the addition of a protease inhibitor cocktail (PIC) (Sigma, USA) for 20 min in an ice bath and processed using an ultrasonic disintegrator Labsonic M (Sartorius, Germany). The homogenates were centrifuged at 16,000 g for 20 min at 4°C. The concentration of total protein in the supernatant was measured using the Total Protein test system (High Technology, USA) on a semi-automated biochemical analyzer BioChem SA (High Technology, USA).

The level of apoptosis, autophagy, and endoplasmic reticulum stress markers in the myocardial tissue of rats was determined using Western blot analysis [19]. The proteins from the lysates (50 µg/sample) were separated into fractions using SDS-PAGE in a vertical chamber (BioRad, USA), utilizing Tris-glycine buffer, pH 8.3 at a voltage of 50V (sample concentration) and 160 V (sample separation). For the identification of protein molecular weights, a mixture of colored protein markers (PageRuler, cat. #26616, Fermentas, Lithuania) was used.

Proteins were transferred from the AA gel to nitrocellulose membranes with a pore size of 0.45 µm (GE Healthcare, Amersham, UK) for 1 h at 4°C. Non-specific binding sites for antibodies were blocked with a 5% solution of skim milk powder (Carnation, USA) in PBST for 2 h at room temperature. After blocking, membranes were incubated with specific antibodies in PBST for 16 h at 4°C. The antibodies used in this study included anti-BAX (1:500, Invitrogen, USA, #UA2671705), anti-Caspase-3 (1:2500, Abcam, USA #ab208161), GRP78 (1:1000, #PA5-34941, Invitrogen, USA), anti-IRE1 (1:800, #PA5-79193, Invitrogen, USA), anti-Beclin-1 (1:1500, Invitrogen, USA, #PA5-20171), anti-beta-Actin (1:5000, Loading Control Monoclonal Antibody (BA3R) (#MA5-15739, Invitrogen, USA). After incubation, membranes were washed in PBST six times for 5 min each and incubated with corresponding secondary antibodies conjugated with horseradish peroxidase for 90 min at room temperature. Non-specifically bound secondary antibodies were washed away with PBST six times. The specific antigen-antibody complex was detected using Enhanced Chemiluminescence (ECL). Visualization of specific staining was performed on Konica Minolta (Medical & Graphic, Inc, Japan) X-ray films. Scanned results of the immunoblotting were subjected to densitometry using the TotalLab TL120 program (Nonlinear Inc., USA). The relative protein content was expressed in arbitrary units (a.u.).

Statistical analysis was performed using Prism 10.2.2 (GraphPad Software Inc., USA) employing one-way ANOVA. Data are presented as mean (M) and standard error of the mean (+SEM). Differences between groups were considered statistically significant at a probability level of $P \leq 0.05$.

Results and Discussion

A broad research interest in the chemical properties and potential therapeutic effects of coordination complexes and supramolecular compounds is fully justified today due to the high demand for the development of new methods and approaches in the treatment of common diseases and pathological conditions. Considering that germanium (a transition metal) and its compounds have low overall toxicity and do not exhibit carcinogenic and teratogenic properties [20, 21], the ability to form coordination bonds makes it a convenient platform for the delivery in the organism of other biologically active compounds in the form of nontoxic coordination complexes. Our recent study on the effects of the nicotinic acid and MIGU-1 on ER stress, autophagy, and apoptosis in the cerebral cortex of rats with chronic ethanol consumption demonstrated that MIGU-1 alleviates ER stress by selectively inhibiting specific apoptotic pathways through the regulation of the autophagy modulator protein Beclin-1 levels [22]. Given the widespread use of NAD^+ in the treatment of cardiovascular diseases [23], we aimed to investigate the potential regulatory effects of MIGU-1 on apoptosis and EP stress in cardiomyocytes in rats with chronic alcohol intoxication.

As is known, the dynamic balance between the synthesis, folding, interaction, and degradation of proteins in a cell is essential for maintaining proper cellular metabolism. The accumulation of misfolded proteins leads to ER stress and the activation of intracellular signaling pathways of the unfolded protein response (UPR) [24]. The UPR's reaction to ER stress plays a protective role in cell survival. UPR removes misfolded proteins through ER-associated degradation (ERAD) or lysosomal degradation. However, under prolonged stress conditions, such as proteotoxicity, UPR sequentially triggers autophagy or apoptosis, which can ultimately lead to the development of various diseases, including cardiovascular diseases, at the organism level [25]. Therefore, in our study, we focused on the ER/UPR signaling path-

way as a mechanism for regulating the survival of cardiomyocytes under conditions of chronic alcohol intoxication.

A key regulator of the UPR system is glucose-regulated protein 78 (GRP78), also known as binding immunoglobulin protein (BiP) [26]. GRP78 functions as a permanent chaperone, facilitating proper protein folding and preventing their aggregation on the one hand. On the other hand, it activates the UPR during the development of ER stress. The activation of the UPR involves three signaling pathways: RNA-dependent protein kinase-like ER kinase (PERK), activating transcription factor 6 (ATF6), and inositol-requiring enzyme 1 (IRE1) pathways [27].

Considering that chronic alcohol consumption is associated with a high risk of developing cardiac hypertrophy and that the level of unprocessed proteins in the ER lumen significantly increases, we investigated the levels of chaperones GRP78 and IRE1 in the myocardium of experimental rats. The study showed that there was no significant difference in the expression levels of GRP78 protein in the myocardium between the control and experimental groups of rats (Fig. 2). The lack of dynamics in the change of GRP78 protein levels in the myocardium of rats may be viewed as a compensatory-adaptive protective mechanism, as the basal expression of GRP78 is crucial for the survival of cardiomyocytes and heart function. Moreover, large fluctuations in GRP78 levels could have critical consequences for cellular metabolism [28].

Among the proteins associated with the UPR, IRE1 is considered the most universal and well-studied branch of the UPR. Recently, IRE1 has been proposed as the main regulator in determining the future fate of the cell under conditions of ER stress [29]. After the accumulation of misfolded and unfolded proteins in the endoplasmic reticulum, the GRP78 protein shifts towards these proteins, changes its spatial conformation and thereby activates the transmembrane protein IRE1. Trans-autophosphorylation of IRE1 is an important regulatory mechanism that controls the activity of this enzyme and its involvement in the cellular response to ER stress [30].

As demonstrated in Fig. 3, *B*, the level of the transmembrane sensory-signaling enzyme IRE1 from the UPR pathway in the myocardium of rats increased by 8.67 times in response to chronic alcohol consumption compared to control rats. The myocardial IRE1 protein level in rats that received MIGU-1 therapy during chronic alcohol intoxication showed a tendency to decrease compared to the pathology group; however, there was no statistically significant difference. At the same time, no differences in the levels of phosphorylated IRE1p protein in the myocardium of animals across all study groups were observed (Fig. 3, *C*).

To investigate the effect of ethanol and MIGU-1 on the IRE1-associated pathway in the myocardium of rats, we analyzed the ratio of phosphorylated IRE1 (IRE1p) to total IRE1. The results of the IRE1p to IRE1 ratio in the myocardium of rats are presented in Fig. 3, *D*. The analysis showed that chronic ethanol consumption reduced the IRE1p/IRE1 ratio by 6.8 times compared to control rats. In the group

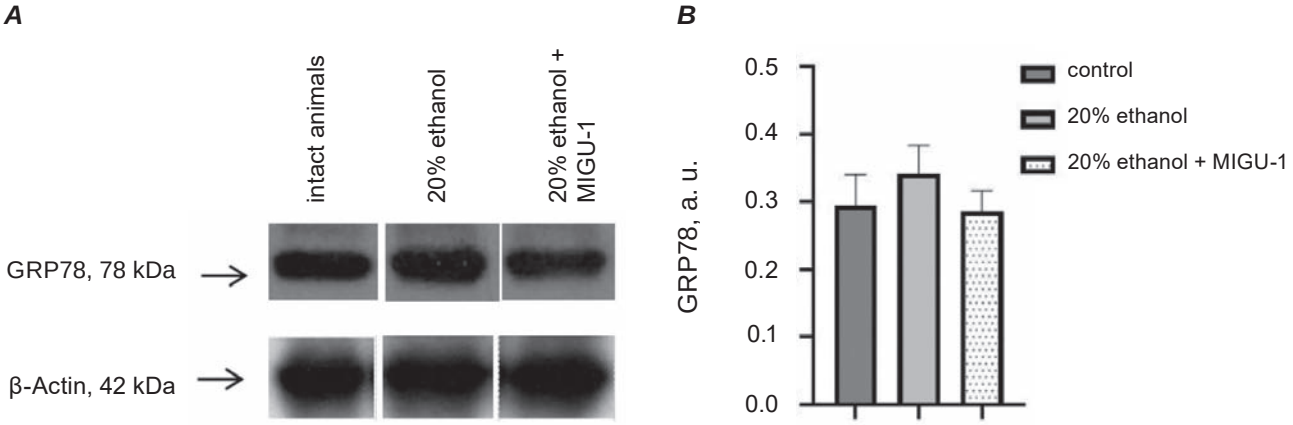

Fig. 2. The GRP78 level in cardiomyocytes of rats with chronic ethanol consumption (20% ethanol) and MIGU-1 treatment (20% ethanol+MIGU-1). ***A*** *– representative immunoblotogram;* ***B*** *– a quantitative expression of GRP78 level in myocardial lysates relative to the β-actin level. Results are shown as mean ± SEM and representative of three independent experiments done in triplicate*

of animals that were administered MIGU-1 during chronic ethanol consumption, the IRE1p/IRE1 ratio in the myocardium was 6.3 times lower compared to control animals (Fig. 3, *D*).

Open scientific sources show that there is a close connection between ER stress and autophagy in the regulation of protein homeostasis and cell survival. On the one hand, ER stress can support intracellular proteostasis by initiating autophagy through signaling molecules of the UPR, such as IRE1 and PERK. On the other hand, the activation of autophagy can reduce the negative effects of ER stress by removing accumulated intracellular protein aggregates and abnormal proteins, thereby promoting cell survival [31]. We investigated the levels of the autophagy marker Beclin 1, which plays a central role in the regulation of autophagy and is a crucial factor in the pathogenesis of cardiac hypertrophy and heart failure [32, 33]. The Beclin-1 level increased 1.59 times in the myocardium of rats after prolonged ethanol consumption compared to control rats (Fig. 4). Administration of MIGU-1 to animals with chronic consumption of 20% ethanol did not affect the Beclin-1 protein level in the myocardium. These results suggest the activation of autophagy as an important protective mechanism for cardiomyocytes against decompensated ER stress in chronic alcohol intoxication. Beclin-1 is a regulator and molecular switch for both autophagy and apoptosis [34]. Cleavage of Beclin-1 by caspase-3 may lead to

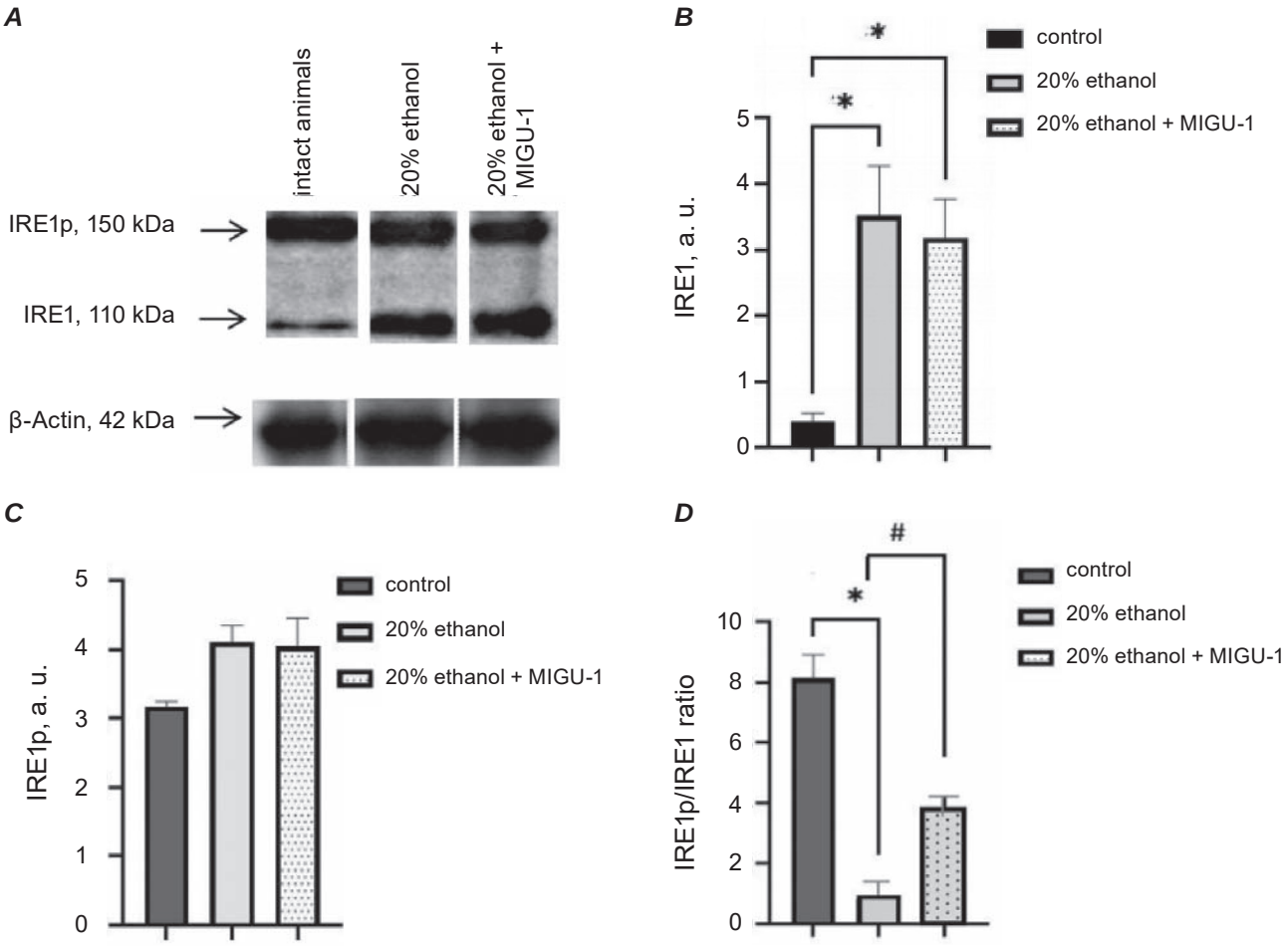

Fig. 3. The level of IRE1 protein and its phosphorylated form IRE1p in cardiomyocytes of rats with chronic ethanol consumption (20% ethanol) and MIGU-1 treatment (20% ethanol+MIGU-1). ***A*** *– representative immunoblotogram;* ***B*** *– a quantitative expression of IRE1 level in myocardial lysates relative to the β-actin level;* ***C*** *– a quantitative expression of IRE1p level in myocardial lysates relative to the β-actin level;* ***D*** *–IRE1/IRE1p ratio. Results are shown as mean ± SEM and representative of three independent experiments done in triplicate; *P < 0.001 vs. control, #P < 0.05 vs. chronic 20% ethanol consumption*

the inactivation of autophagy, resulting in enhanced apoptosis. Interestingly, caspase-mediated cleavage of Beclin-1 contributes to the cross-talk between apoptosis and autophagy [35].

The level of caspase-3 in the rat myocardial tissue from all experimental groups did not differ significantly from each other (Fig. 5, *B*). However, the level of cleaved caspase-3 in the rat myocardial tissue in response to ethanol consumption increased 4.39 times compared to control group (Fig. 5, *C*). Administration of MIGU-1 resulted in a correction of the cleaved caspase-3 level compared to the group with chronic ethanol consumption. Western blot analysis showed that chronic consumption of 20% ethanol and the administration of MIGU-1 in the context of ethanol intake significantly decreased the ratio of cleaved caspase-3 to procaspase-3 in the myocardial tissue of the rats (Fig. 5, *D*).

Considering that ethanol induces mitochondria-dependent apoptosis pathways by causing overexpression of the pro-apoptotic protein BAX and activation of caspase-3, we examined the levels of BAX dimer in the myocardium of rats [36]. The levels of BAX dimer in the myocardium of rats with chronic ethanol consumption were 1.36 times higher compared to the control group, Fig. 6. Administration of MIGU-1 did not significantly affect the level of BAX dimer in the myocardium of rats with chronic ethanol consumption (Fig. 6).

In summary, the chronic alcohol intoxication induced ER stress-associated activation of both apoptotic factors (cleavage of caspase-3 and accumulation of Bax protein) and overexpression of Beclin-1, indicating an enhancement of autophagy in rat cardiomyocytes. The interaction between autophagy and apoptosis plays a crucial role in overcoming the consequences of endoplasmic reticulum stress and ensuring cell survival, which does not preclude either individual or simultaneous activation of these processes [37, 38]. It is also noteworthy that the expression level of GRP78, a key marker of endoplasmic reticulum stress and a regulator of UPR signaling activation, remained significantly unchanged in the rat myocardial tissue of rats subjected to chronic ethanol administration. Furthermore, the ratio of IRE1p to IRE1 was significantly lower in alcoholized rats, indicating a reduction in the activation of the IRE1 signaling pathway of the UPR (Fig. 3, *D*).

It is known that nicotinic acid is viewed not only as a functional water-soluble coenzyme but also as a cardioprotective agent [39]. The complexation of nicotinic acid with germanium in the form of a coordination compound has enhanced the activity of nicotinic acid and opened up new potential effects for cytoprotective activity under various types of intoxication. Our earlier studies on the pharmacological effects of MIGU-1 demonstrated the antioxidant properties of the nicotinic acid-germanium complex in a model of doxorubicin-induced cardiomyopathy [40] and its neuroprotective effects under conditions of chronic ethanol consumption [22]. Similar to its

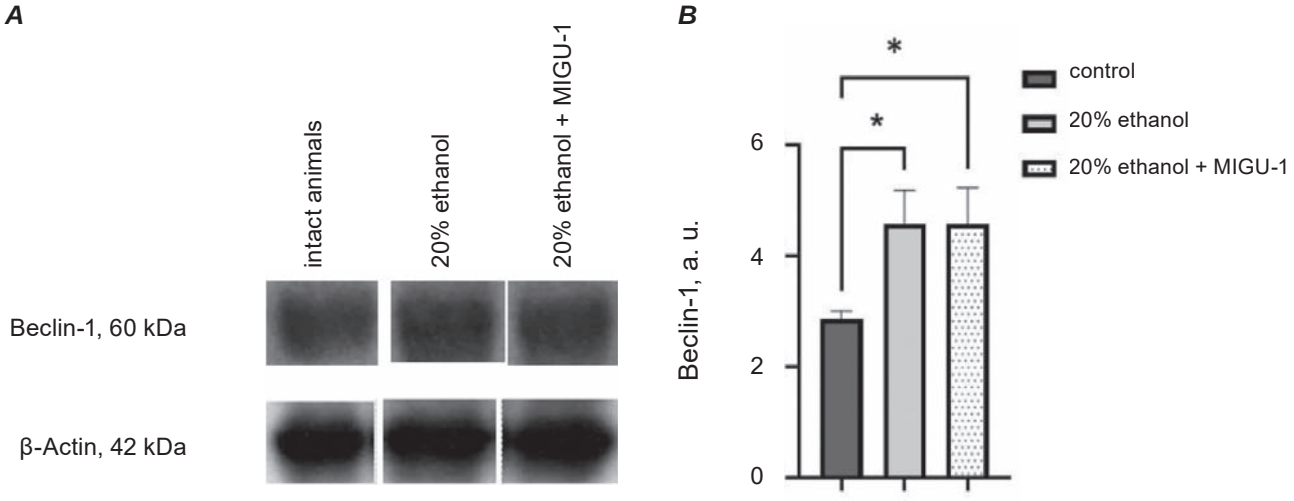

Fig. 4. The Beclin-1 level in cardiomyocytes of rats with chronic ethanol consumption (20% ethanol) and MIGU-1 treatment (20% ethanol+MIGU-1). ***A*** *– representative immunoblotogram;* ***B****– a quantitative expression of GRP78 level in myocardial lysates relative to the β-actin level. Results are shown as mean ± SEM and representative of three independent experiments done in triplicate; *P < 0.05 vs. control*

effects on the nervous tissue of rats with chronic alcohol intoxication, this study showed that MIGU-1 minimizes ethanol-induced impairments in the cardiomyocytes of alcoholized animals by inhibiting the activation of caspase-3. In our opinion, the antiapoptotic action of MIGU-1 under chronic toxic exposure to alcohol in both nervous tissue and myocardium is due to the synergistic effect of nicotinic acid and germanium in protecting cells from programmed cell death. Nicotinic acid is known for its antioxidant properties, which aim to reduce reactive oxygen species, stabilize mitochondrial membranes, and inhibit the activation of executioner caspases [41, 42]. Germanium, in its simple compounds, prevents the development of tissue hypoxia, positively affecting energy metabolism and preventing cellular energy depletion [8, 43]. MIGU-1 may serve as an effective tool in the prevention and adjunct therapy of various diseases, including cardiovascular and neurodegenerative disorders. Future research will help further elucidate the regulatory potential and therapeutic effects of MIGU-1 in correcting pathological changes in cardiac muscle induced by the toxic effects of ethanol.

Conclusions. Chronic ethanol consumption leads to an apoptotic switch in UPR function by blocking the phosphorylation of IRE1 in cardiomyocytes, which was accompanied by an increase in

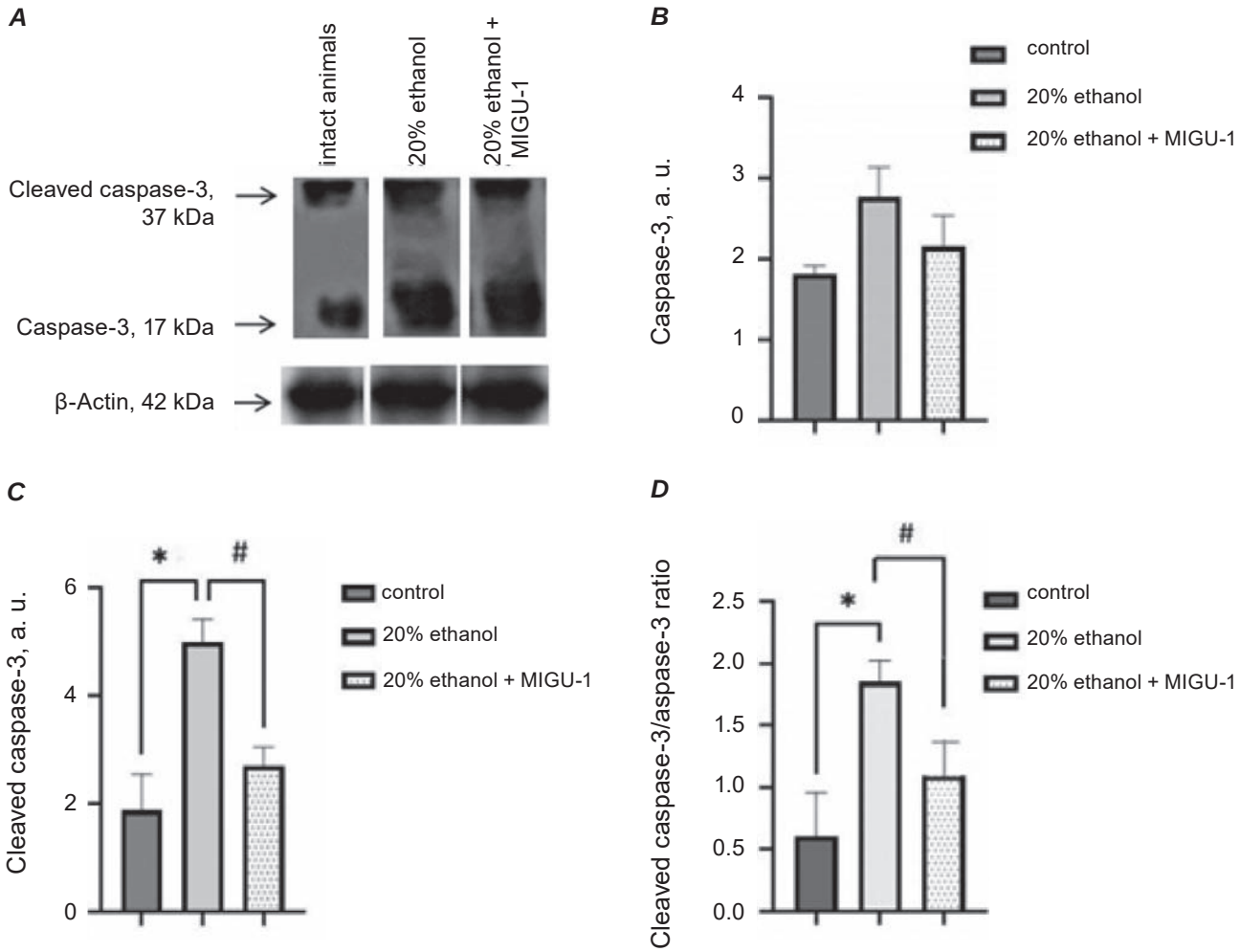

Fig. 5. The level of caspase-3 protein and cleaved caspase-3 proteins in cardiomyocytes of rats with chronic ethanol consumption (20% ethanol) and MIGU-1 treatment (20% ethanol+MIGU-1). ***A*** *– Representative immunoblotogram;* ***B*** *– a quantitative expression of caspase-3 level in myocardial lysates relative to the β-actin level;* ***C*** *– a quantitative expression of cleaved caspase-3 level in myocardial lysates relative to the β-actin level;* ***D*** *– cleaved caspase-3/caspase-3 ratio. Results are shown as mean ± SEM and representative of three independent experiments done in triplicate; *P < 0.001 vs. control, #P < 0.05 vs. chronic 20% ethanol consumption*

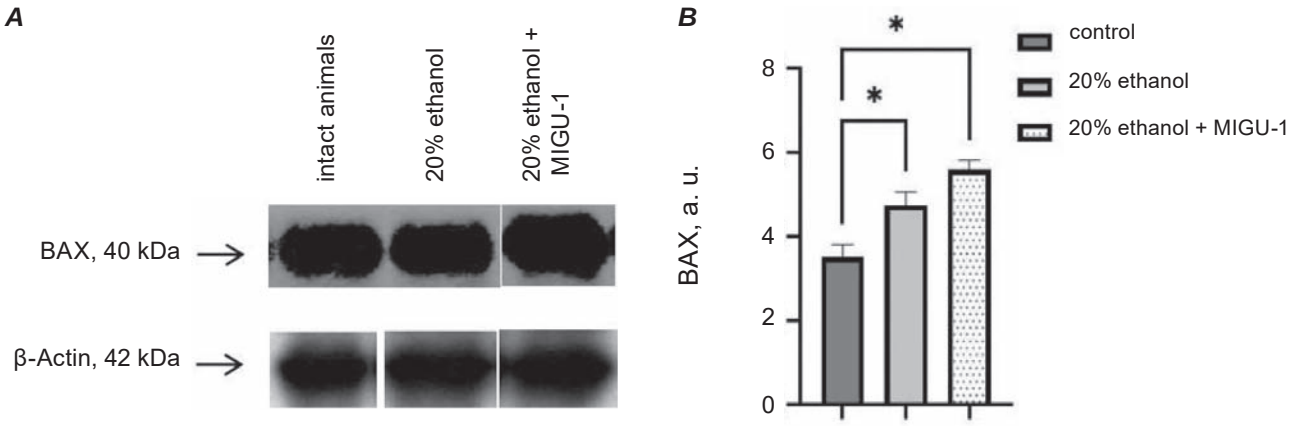

Fig. 6. The BAX-dimer level in cardiomyocytes of rats with chronic ethanol consumption (20% ethanol) and MIGU-1 treatment (20% ethanol+MIGU-1). ***A*** *– representative immunoblotogram;* ***B*** *– a quantitative expression of BAX dimer level in myocardial lysates relative to the β-actin level. Results are shown as mean ± SEM and representative of three independent experiments done in triplicate; *P < 0.05 vs. control*

the level of BAX protein and cleaved caspase-3. In parallel, we found an ethanol-associated evaluation in the Beclin-1 level and the absence of a difference in the content of the protein GRP78 in the myocardium of all studied groups of animals, which indicated an increase in the role of autophagy in cardiomyocytes in a condition of alcohol intoxication. The nicotinic acid-germanium complex (MIGU-1) exhibits anti-apoptotic effects and promotes cardiomyocyte survival, reducing ER stress while regulating the balance between apoptotic and autophagic factors in prolonged consumption of 20% ethanol. Further investigation into the effects of MIGU-1 on cell survival mechanisms in the presence of ethanol will contribute to the search for new approaches to the prevention and adjunct therapy of diseases associated with the toxic effects of chronic alcohol consumption.

Conflict of interest. The authors have completed the Unified Conflicts of Interest form at http://ukrbiochemjournal.org/wp-content/uploads/2018/12/coi_disclosure.pdf and declare no conflict of interest.

Funding. This study was conducted without financial support.

БІОМАРКЕРИ АПОПТОЗУ ТА СТРЕСУ ЕНДОПЛАЗАТИЧНОГО РЕТИКУЛУМУ КАРДІОМІОЦИТІВ ЩУРІВ ЗА ХРОНІЧНОГО ВЖИВАННЯ ЕТАНОЛУ ТА ВВЕДЕННЯ ГЕРМАНІЄВО-НІКОТИНОВОГО КОМПЛЕКСУ

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Хронічне споживання етанолу пов'язане з низкою шкідливих впливів на різні системи організму, включаючи серце. Координаційні комплекси біоактивних сполук на основі нетоксичних металів викликають інтерес у біомедичних дослідженнях завдяки їх потенційним терапевтичним властивостям. Метою дослідження була оцінка впливу комплексу германій-нікотинової кислоти (МІГУ-1) на показники апоп-

тозу та стресу ендоплазматичного ретикулума (ЕР) у міокарді щурів за хронічної дії етанолу. Самиць щурів лінії Вістар було поділено на 3 групи по 6 тварин у кожній: інтактні тварини; щури, які отримували 20% етанол як єдине джерело рідини протягом 110 днів; тваринам із хронічним споживанням 20% етанолу, яким з 90-ї доби до кінця досліду внутрішньочеревно вводили розчин МІГУ-1 (10 мг/кг/добу). Біомаркери, пов'язані з апоптозом, аутофагією та ЕР стресом, оцінювали за допомогою Вестерн-блот аналізу. Показано, що хронічне вживання етанолу значно активізувало проапоптотичні шляхи у тканині міокарда щурів, про що свідчив підвищений вміст протеїнів розщепленої форми каспази-3 та BAX, у той час як зростання рівня протеїну Beclin-1 вказувало на посилення аутофагії. Виявлено достовірне зниження вмісту протеїну IRE1 та його фосфорильованої форми у міокарді без змін рівня протеїну GRP78. За терапевтичного введення комплексу МІГУ-1, спостерігали як зниження інтенсивності індукованого етанолом апоптозу, так і ослаблення ER-стресу в кардіоміоцитах, проте рівень протеїнів Beclin-1 і GRP78 залишався сталим. Зроблено висновок, що комплекс МІГУ-1 сприяє виживанню кардіоміоцитів шляхом балансування активності апоптозу та системи відповіді незгорнутим протеїнам і запобігає ушкодженням серця у разі надмірного споживання алкоголю.

Ключові слова: нікотинова кислота, германій, МІГУ-1, інтоксикація алкоголем, кардіоміоцити щурів, апоптоз, стрес ЕПР, аутофагія.

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