ASTAXANTHIN PROTECTS HEART MITOCHONDRIA FROM DAMAGE CAUSED BY CHRONIC ALCOHOL INTOXICATION

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The natural antioxidant astaxanthin (AST) demonstrates the cardioprotective effect on cardiac mitochondria in rats subjected to chronic alcohol intoxication. Particularly, AST restored cardiac mitochondrial respiratory activity and Ca^{2+} capacity of rats exposed to chronic alcohol intoxication; it also had a positive impact on the balance of functionally important processes of mitochondrial fission/fusion, as well as mitophagy. In addition, AST prevented alcohol-induced morphological damage to cardiac tissue. Overall, the results demonstrate that AST promotes normalization of cardiac mitochondrial function, protecting these organelles from degenerative changes caused by alcohol intoxication and improving cardiac energy metabolism. Thus, AST helps to compensate the cardiac mitochondrial damage caused by chronic alcohol intake by restoring their functional activity and stress resistance.

Keywords: mitochondrial dysfunction; chronic alcohol intoxication; astaxanthin; cardiac mitochondria; mitophagy; mitochondrial fission/fusion

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INTRODUCTION

Pathological disorders in the cardiovascular system functioning represent urgent problems in modern cardiology. The consequences of alcohol abuse on the heart can manifest as heart rhythm disturbances, arterial hypertension, and lead to the development of extremely dangerous diseases such as alcoholic ketoacidosis, coronary heart disease, and alcoholic cardiomyopathy [1].

Alcoholic cardiomyopathy is the most dangerous consequence of chronic alcohol exposure on the cardiovascular system. It manifests itself as severe structural damage to the heart muscle due to the toxic effects of alcohol on the myocardium [2]. The proposed mechanisms leading to the development of alcoholic cardiomyopathy include the interconnected cellular processes of mitochondrial metabolism, oxidative stress and apoptosis. Pathological changes induced by alcohol affect the structure and morphology of mitochondria. Mitochondria have a unique ability to undergo cycles of fission and fusion to adequately respond to altered metabolic needs of the cell [3, 4]. The balance between these processes maintains normal mitochondrial functioning. The key regulators of mitochondrial dynamics include: dynamin-related protein1 DRP1, responsible for division; mitofusin 2 (Mfn2), which controls the fusion of outer membranes; optic atrophy protein 1 (OPA1), which regulates the fusion of inner mitochondrial membranes [5]. Various stress factors, including the toxic effects of alcohol, cause an imbalance in the processes of mitochondrial fission and fusion; this leads to their pathological fragmentation and dysfunction of these organelles [6, 7]. In addition, alcohol intoxication leads to changes in the respiratory and ATP-synthesizing activity of mitochondria [8, 9]. The degenerative effects of chronic alcohol intoxication leadto impairments in the mitophagy system (the process of removing damaged mitochondria). Normally, mitophagy processes are controlled by PINK1/Parkin marker proteins [10]. Mitochondrial dysfunction (including alcohol-induced dysfunction) leads to an imbalance in the PINK1/Parkin system, which reduces the efficiency of removing damaged mitochondria, thus worsening mitochondrial dysfunction and contributing to the development of alcoholic cardiomyopathy and other diseases [11, 12].

The diversity and contradictory nature of existing hypotheses indicate persistent gaps in our understanding of the precise molecular mechanisms underlying alcohol effects on mitochondria, particularly their bioenergetic functions. Since mitochondrial dysfunction is directly linked to oxidative stress, numerous antioxidants, both natural and synthetic, are extensively studied for their ability to protect mitochondria from oxidative damage and promote the restoration of their functional activity [13, 14].

Abbreviations used: AST – astaxanthin; PINK1 – PTEN-induced kinase 1; DRP1 – dynamin-related protein 1; Mfn2 – mitofusin 2; RCR – respiratory control ratio; ETC – electron transport chain.

These compounds are considered as promising therapeutic agents for the treatment and prevention of mitochondria-targeted diseases, including those associated with alcohol consumption.

Although the effects of many of these compounds on mitochondria have been well studied, new information has recently emerged regarding the efficacy and mechanisms of action of some of them, opening the door to new technologies for therapeutic strategies and repositioning existing drugs for the treatment of new diseases. For example, the natural antioxidant astaxanthin (AST) has demonstrated high efficacy in the treatment and prevention of mitochondria-related diseases [8, 9, 15–17]. Our group has shown that AST can prevent alcohol-induced liver mitochondrial dysfunction [8, 9] and can effectively restore cardiac mitochondrial function after isoproterenol-induced damage [15, 16].

The aim of this study was to investigate the efficacy of AST in preventing ethanol-induced impairment of cardiac mitochondrial function and structure in rats.

MATERIALS AND METHODS

Reagents

The following reagents were used in this study: animal feed mixtures (control and alcohol) (BioServ, USA); 5% AST solution (Natural, China) (administered at a dose of 150 mg/kg); mitochondrial isolation media containing: 75 mM sucrose, 10 mM Tris-HCl (pH 7.4), 225 mM mannitol, 0.5 mM EDTA, 0.5 mM EGTA, 0.1% BSA (all reagents from Sigma-Aldrich, USA); incubation medium containing: 125 mM KCl, 10 mM Tris (pH 7.4), 2 mM K_2HPO_4, 5 mM glutamate, 5 mM malate (all reagents from Sigma-Aldrich); Laemmli buffer (Bio-Rad, USA), Roti-Block (Carl Roth, Germany), O.C.T. Compound Tissue Tek (Sakura; Japan).

Antibodies

The following antibodies were used: the OXPHOS monoclonal antibody cocktail (Abcam, UK): CV-ATP5A (55 kDa), CIII-UQCRC2 (48 kDa), CIV-MTCO1 (40 kDa), CII-SDHB (30 kDa), CI-NDUFB8 (20 kDa), polyclonal antibodies: DRP1 (Elabscience, USA), MFN2 (Elabscience, China), OPA1 (Cloud-Clone Corp., China), PINK1 (Cusabio, China), Parkin (Abclonal, China), Tom20 (loading control) (Cell Signaling, USA), secondary antibodies conjugated to HRP (Bio-Rad), ECL (Bio-Rad).

Equipment and Consumables

These included: the nitrocellulose membrane (0.2 μm) (Bio-Rad); a set of marker proteins (10–250 kDa) (Bio-Rad).

Software and Systems

These included: Nis Elements AR4.13.05 (Build933) (Nikon, Japan), Image Lab (Bio-Rad).

Animals and their Treatments

The methods used are described in detail in [9]. Animals obtained from the vivarium at the Institute of Theoretical and Experimental Biophysics of the Russian Academy of Sciences were maintained under standard conditions approved in this vivarium, including the diet, light/dark cycle, temperature, and humidity. Wistar rats of the same age and weight were housed individually in cages with a controlled temperature (23±2°C) and a 12-h lighting cycle. Each cage was equipped with graduated water dispensers. The study included three groups of animals, 5 rats in each group (15 animals in total): group 1 — control, group 2 — animals receiving a special feed with the addition of ethanol, group 3 — animals receiving a special feed with ethanol and AST ("Natural"). The number of animals included in the calculations was determined on the basis of the statistical reliability of the results obtained and confirmed by preliminary experiments. Chronic alcoholism in animals of groups 2 and 3, was modelled mixture was diluted with the appropriate amount of ethanol and water (for control animals only water). The diet contained the same amount of proteins and fats. Animals in the control group and in groups 2 and 3 received equivalent amounts of food. The concentration of ethanol in groups 2 and 3 was gradually using the Lieber-DeCarli diet [18]. The feed mixtures were from BioServ. The control mixture of 5% AST (150 mg/kg) dissolved in olive oil. Rats in groups 1 and 2 received olive oil contained fats (35%), proteins (18%), and carbohydrates (47%). The alcohol diet was a dry mixture in which 36% of calories from carbohydrate components were replaced by calories from ethanol (concentration in the final diet was 5%); the concentrations increased (0%, 1%, 2%, 3%, 4%, and 5%) over 10 days to induce habituation. Then, for 8 weeks, animals in groups 2 and 3 received food with 5% ethanol. In addition, animals in group 3 received 5% AST (150 mg/kg) dissolved in olive oil orally. Rats in groups 1 and 2 received olive oil in equal quantities as a vehicle. Details of AST administrations (5%, 150 mg/kg) have been described in [17, 19].

Histological Analysis of Left Ventricular Tissue Sections

After removing the heart from the chest cavity, a fragment of the left ventricle was excised with a scalpel and washed with cold phosphate-buffered saline. The samples were fixed in neutral formalin for 24 h at room temperature using standard procedures. After fixation, the fragments were washed

three times with distilled water to remove excess of phosphate and immersed in O.C.T. (Optimal Cutting Temperature) Compound Tissue Tek (Sakura) for 12 h at 4°C. Cross sections (7 μm thick) were prepared using a Shandon CRYOTOME 620E (Thermo Fisher Scientific, USA) at 30 μm intervals. Each series of three sequential sections was stained with hematoxylin and eosin (H&E) and the differential trichrome method according to Lilly [20]. To obtain a general picture of the alcohol-induced cardiac tissue damage, histotopograms were obtained on a Nikon Eclipse Ti-E microscopy system (Nikon) using Nis Elements AR4.13.05 (Build933) software.

Isolation of Rat Heart Mitochondria

Mitochondria were isolated from whole rat hearts of each animal by using the standard method described in [21]. The hearts were minced, freed from blood vessels, and homogenized in a medium containing 75 mM sucrose, 10 mM Tris-HCl (pH 7.4), 225 mM mannitol, 0.5 mM EDTA, 0.5 mM EGTA, and 0.1% BSA. The homogenate was centrifuged at 1000 *g* for 10 min. Mitochondria contained in the supernatant were then sedimented at 8500 *g* for 10 min. Mitochondria (in the pellet) were then washed with EDTA- and BSA-free isolation medium at 8500 *g* for 10 min and suspended in the same medium. All procedures were performed at 4°C. Mitochondrial protein content, determined by the Bradford method [22], was 30–35 mg/ml.

Determination of Mitochondrial Function

A suspension of isolated rat heart mitochondria (1 mg protein/ml) was placed in a multifunctional chamber with built-in electrodes: a Clark type O_2 electrode and a Ca^{2+}-selective electrode (Niko-Analit, Russia) [23]. The mitochondrial suspension was incubated at 25°C in a medium containing 125 mM KCl, 10 mM Tris (pH 7.4), 2 mM K_2HPO_4, and glutamate (5 mM) and malate (5 mM) as respiratory substrates. Oxygen consumption rates ($V_{st.2}$, $V_{st.3}$, $V_{st.4}$, V_u) were measured in a closed chamber after adding 200 μM ADP to the mitochondria and were expressed as ng-atom O $min^{-1} \cdot mg^{-1}$ protein. The mitochondrial Ca^{2+} capacity was determined using a Ca^{2+}-sensitive electrode as the amount of Ca^{2+} loaded into the mitochondria. Each Ca^{2+} addition was 25 nmol per mg protein.

Electrophoresis and Western Blot Analysis

Aliquots of native mitochondria isolated from each experimental group were solubilized in Laemmli sample buffer (Bio-Rad) (2 mg/ml). The samples were heated to 95°C for 5 min. Twenty micrograms of mitochondrial lysate were loaded onto each lane of the gel. Bio-Rad marker kits containing marker proteins from 10 kDa to 250 kDa were used as markers. Mitochondrial proteins were separated by molecular mass using 12.5% SDS-PAGE. Proteins were transferred from the gel to a nitrocellulose membrane (0.2 μm, Bio-Rad) using a semi-dry transfer apparatus (Bio-Rad) for Western blot analysis. The membranes were then blocked using Roti-block solution (Carl Roth) for 1 h. After blocking, the membranes were stained with commercial antibodies in accordance with the instructions for their use of the antibodies.

The following antibodies were used in the study: OXPHOS monoclonal antibody cocktail (Abcam), consisting of the alpha subunit of complex V (CV-ATP5A, 55 kDa), cytochrome *b-c1* complex subunit 2 of complex III (CIII-UQCRC2, 48 kDa), mitochondrially encoded cytochrome *c* oxidase I complex IV (CIV-MTCO1, 40 kDa), succinate dehydrogenase complex II subunit B (CII-SDHB, 30 kDa), NADH dehydrogenase [ubiquinone] 1 beta subunit subcomplex 8 of complex CI (CI-NDUFB8, 20 kDa); polyclonal antibodies to DRP1 (Elabscience, USA), mitofusin 2 (Elabscience, China), OPA1 (Cloud-Clone Corp.), PINK1 (Cusabio), Parkin (Abclonal). Polyclonal antibodies to the mitochondrial outer membrane protein Tom20 (translocase of outer mitochondrial membrane; Cell Signaling) were used as a control for protein loading. Immunoreactivity was determined using secondary antibodies conjugated with horseradish peroxidase (Bio-Rad). Peroxidase activity was determined with ECL (Bio-Rad) using the ChemiDoc Touch imaging system (Bio-Rad). Protein bands were quantified using densitometry (Image Lab software, Bio-Rad) as the ratio of the optical density of proteins to that of proteins used as a protein loading control (Tom20).

Statistical Analysis

Statistical analysis was performed using mean values ± standard deviation (SD) from at least four to six independent experiments. Analysis of variance (ANOVA) with the appropriate post-hoc test (Student-Newman-Keuls) was used to compare the statistical significance of results between groups. Differences were considered statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

Since the pathological effects of alcohol are highly variable and affect virtually all organs and tissues, diseases caused by chronic ethanol consumption are characterized by a wide variety of clinical forms and affected organs. The detrimental effects of alcohol on the liver, as the body first filter for toxins and the primary site of ethanol metabolism, are well known. However, ethanol consumption

is equally harmful to other organs, including the nervous [24] and cardiovascular [25] systems. Good evidence now exists that alcohol-related pathological changes in organs and tissues are based on mitochondrial dysfunction, associated with the development of oxidative stress and disturbances in the fatty acid oxidation systems, oxidative phosphorylation, and the generation of reactive oxygen species (ROS) [8, 9, 26–28]. Consequently, cardiac mitochondria, as the main energy "suppliers", are also primarily exposed to the detrimental effects of alcohol. Previously, our laboratory first discovered the protective effect of the natural antioxidant AST on ethanol-induced damage to rat liver mitochondria [8, 9]. Therefore, in the present study, we have investigated the potential cardioprotective effect of AST in alcohol-induced mitochondrial degeneration.

Three groups of animals were selected to study the effect of AST on cardiac mitochondria in rats exposed to chronic alcohol intoxication: group 1 (control), group 2 (ethanol-treated), and group 3 (ethanol and AST-treated). To compare the physiological characteristics of animals in the different groups, we analyzed body and heart weight, as well as blood alcohol levels. The obtained values are presented in Table 1.

It should be noted that at the beginning of the experiment, all animals had approximately the same weight (160±2 g). Table 1 shows that at the end of the experiment, rats in group 2 (ethanol-treated) weighed less than rats in the other groups, while the hearts of group 2 rats weighed significantly more. At the same time, these parameters in group 3 rats (ethanol and AST-treated) were comparable to those in the control group. It should also be noted that the average blood alcohol content in groups 2 and 3 rats was 0.85 g/l, corresponding to a moderate degree of intoxication. These data suggest the development of alcohol-associated degenerative changes in the heart in the experimental animals. These changes indicate the pathogenic effects of alcohol on the heart, manifested by structural and functional impairments.

To assess the extent and nature of myocardial damage and to identify the location of the lesion, transmural histotopograms of left ventricular samples from all groups were obtained. Identical sections of the left ventricle (LV) of the rat heart were collected from animals of each experimental group for analysis. To assess the extent and nature of cardiac tissue damage in rats subjected to alcohol intoxication and the possible protective effect of AST, histotopograms of transverse ventricular sections stained using the Lilly differential staining method [20] (allowing identification of muscle and collagen fibers) were analyzed. Figure 1 shows control rat cardiac tissue samples, the state of cardiac tissue after chronic alcohol administration, and cardiac tissue sections after chronic AST administration and alcohol intoxication. As can be seen in Figure 1, no significant changes in the histoarchitecture or structure of cardiac tissue were detected compared to animals in the control group. Furthermore, analysis of the tissue extracellular matrix, particularly collagen fibers, revealed no signs of fibrosis in any group.

Figure 1b shows results of detailed examinations of myofibrils and cardiomyocytes in the left ventricular tissue of the heart of each group of rats performed using hematoxylin and eosin (H&E) staining. In the control group (Group 1), myofibrils had a normal smooth structure, and the cardiomyocyte nuclei were oval in shape and located in the center of the cells (Fig. 1b, control group). Under conditions of alcohol intoxication, areas of swelling of the cardiomyocyte cytoplasm were observed (Fig. 1b, in the center). The latter is a sign of damage associated with possible disruption/dysfunction of the heart vessels (areas are shown by yellow arrows). At the same time, in tissue samples of group 3 animals (AST + ethanol), similar areas of swelling of the cardiomyocyte cytoplasm were not detected (Fig. 1b, right), and the structure of myofibrils in this experimental group basically corresponded to that in the control group. Thus, it is reasonable to suggest that AST has cardioprotective properties, protecting cardiac tissue structure from damage caused by alcohol intoxication. The AST action likely contributes to a reduction

Table 1. Changes in biometric parameters of treated with ethanol and AST

Parameter	1 (Control)	2 (Ethanol)	3 (AST + Ethanol)
Body mass, g	400.2±19.44	331.0±15.1*	394.8±18.1$^{\#}$
Heart mass, g	2.1±0.3	3.33±0.3*	1.9±0.9$^{\#}$
Heart mass/body mass ratio, %	2.9±0.2	3.8±0.3*	2.9±0.1$^{\#}$
Ethanol content, g/l	—	0.9±0.1*	0.8±0.1*

Data represent mean ± SD of 5 independent experiments. * $p < 0.05$ – statistically significant difference in values compared to the control (group 1). $^{\#}$ $p < 0.05$ – statistically compared to cardiac mitochondria isolated from ethanol treated rats (group 2). The statistical significance of differences between pairs of mean values was assessed using the Student-Newman-Keuls test.

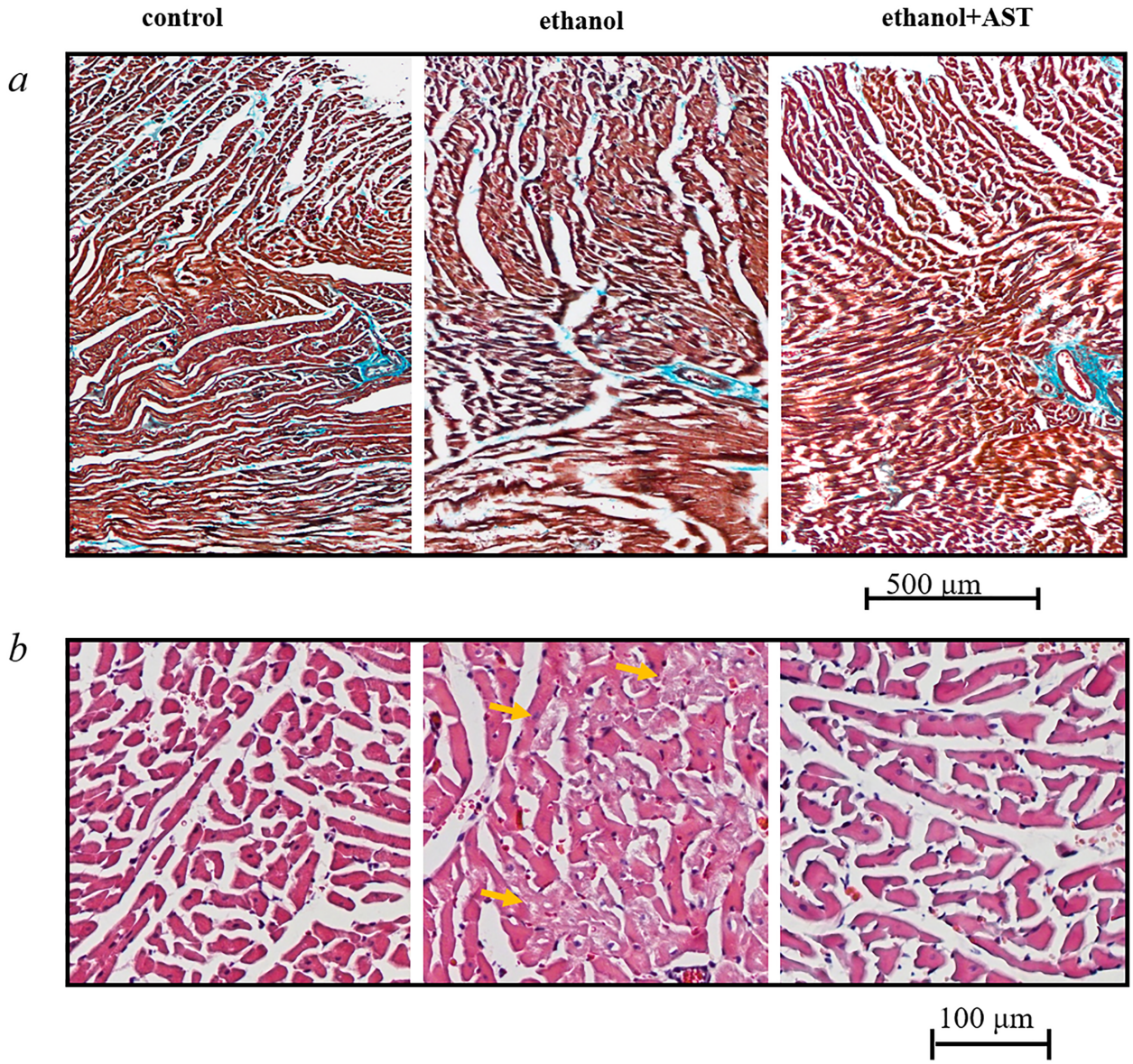

Figure 1. Histotopogram fragments of the rat heart left ventricle. Light microscopy: **a** – Lilly trichrome staining, scale bar = 500 μm; **b** – hematoxylin and eosin staining (H&E: cell nuclei are highlighted in purple, erythrocytes in red, cell cytoplasm in pink), scale bar = 100 μm. Arrows indicate sites of cytoplasmic swelling. A color version of the figure is available in the online version of the journal.

in oxidative stress and inflammatory processes, thus preventing ethanol-induced morphological and functional impairments of the myocardium.

Mitochondria are known to accumulate excess cytoplasmic calcium, and their ability to accumulate calcium reflects their functional reserves and adaptive capacity. Being a critical component of intracellular signaling, Ca^{2+} can regulate critical biochemical processes within the cell, maintaining cell functioning or, conversely, leading to cell death [29, 30]. High Ca^{2+} capacity suggests preserved mitochondrial function and the ability to regulate intracellular calcium homeostasis, whereas a decrease in this capacity is associated with impaired energy metabolism, increased oxidative stress, and the initiation of cell death mechanisms, for example, through the formation of high-permeability pores in mitochondria [30]. Since changes in mitochondrial Ca^{2+} capacity are used to assess the extent of mitochondrial damage and the effectiveness of compensatory-adaptive responses, for example, during hypothermia, ischemia, infarction, or alcohol intoxication [29, 30], we have investigated changes in the Ca^{2+} capacity of rat heart mitochondria under our experimental conditions. Figure 2a shows the curves of changes in Ca^{2+} transport in mitochondria isolated from all experimental groups (each Ca^{2+} addition was 25 nmol per mg protein), and Figure 2b shows the quantitative parameters of Ca^{2+} capacity. As shown in Figure 2a, the first

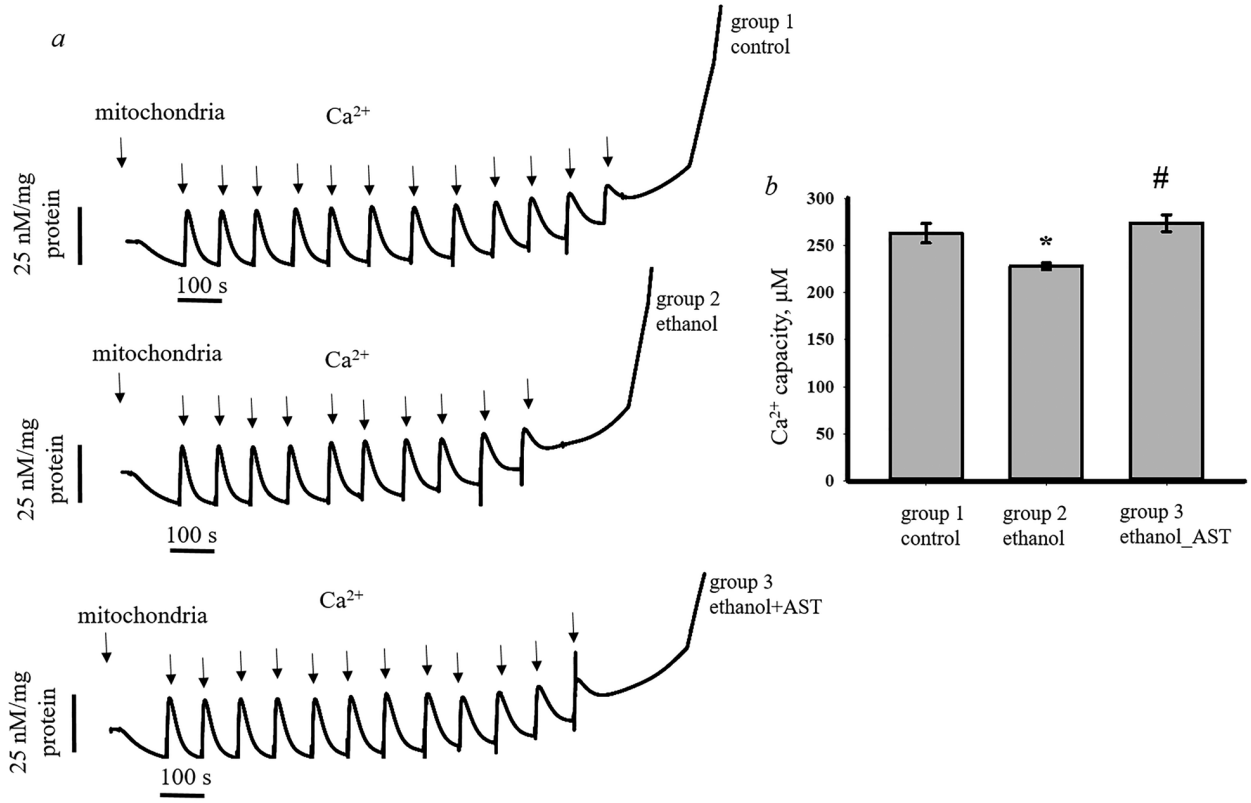

Figure 2. Effect of AST on changes in mitochondrial Ca^{2+} capacity in rat hearts during alcohol intoxication. **a** – curves characterizing changes in Ca^{2+} fluxes in mitochondria isolated from all experimental groups; **b** – quantitative analysis of Ca^{2+} capacity. Each Ca^{2+} addition was 25 nmol per mg of mitochondrial protein. Panel **a** shows the results of a typical experiment, panel **b** shows the average values of six independent experiments. * $p < 0.05$ significant difference relative to the control group, # $p < 0.05$ significant difference relative to the ethanol group.

addition of Ca^{2+} to cardiac mitochondria isolated from animals of each group resulted in the accumulation of Ca^{2+} in the mitochondria. However, the twelfth addition of Ca^{2+} to mitochondria from the control group, the tenth addition of Ca^{2+} to mitochondria from group 2, and the twelfth addition of Ca^{2+} to mitochondria from group 3 resulted in Ca^{2+} release from the mitochondria. Figure 2b shows that mitochondria from the control group were able to take up and retain 263±23.0 nmol Ca^{2+}/mg protein. The mitochondrial capacity of group 2 animals decreased to 228±3.4 nmol/mg protein; thus, ethanol consumption reduced the Ca^{2+} capacity in cardiac mitochondria by 14% relative to the control. The mitochondrial capacity of group 3 animals (treated with AST and ethanol) remained within control values (273±9.0 nmol/mg protein). Thus, we can conclude that AST restores mitochondrial Ca^{2+} capacity reduced by ethanol. This indicates that AST promotes restoration of mitochondrial Ca^{2+} capacity, thus maintaining their functional viability and stabilizing intramitochondrial calcium homeostasis. The AST action reduces mitochondrial membrane permeability by preventing the opening of the non-specific mitochondrial permeability transition pore (mPTP). This protects mitochondria from swelling and destruction.

It has previously been shown that chronic alcohol consumption leads to disturbances in the oxidative phosphorylation system and also negatively affects mitochondrial respiration and the efficiency of ATP production [31, 32]. Next, we examined the effect of AST on the parameters of oxidative phosphorylation of rat cardiac mitochondria during alcohol intoxication. For this purpose, the rate of mitochondrial oxygen consumption and the respiratory control ratio (RCR) were determined at various stages (Fig. 3).

Figure 3a shows the curves reflecting changes in the oxygen consumption rate in State 2 ($V_{st.2}$, substrate-dependent respiration), State 3 ($V_{st.3}$, the mitochondria oxygen consumption rate in the phosphorylated state), State 4 ($V_{st.4}$, the respiration rate after depletion of excess ATP) and the oxygen consumption rate during mitochondrial uncoupling (V_u). Quantitative characteristics of the oxygen consumption rate in different states and respiratory control ratio (RCR, defined as the ratio $V_{st.3}/V_{st.4}$, which reflects the efficiency of mitochondria in stimulating oxidative phosphorylation and the relationship between oxygen consumption and ATP production) are presented in Figure 3b–f. Figure 3b,c shows that in heart mitochondria of rats exposed

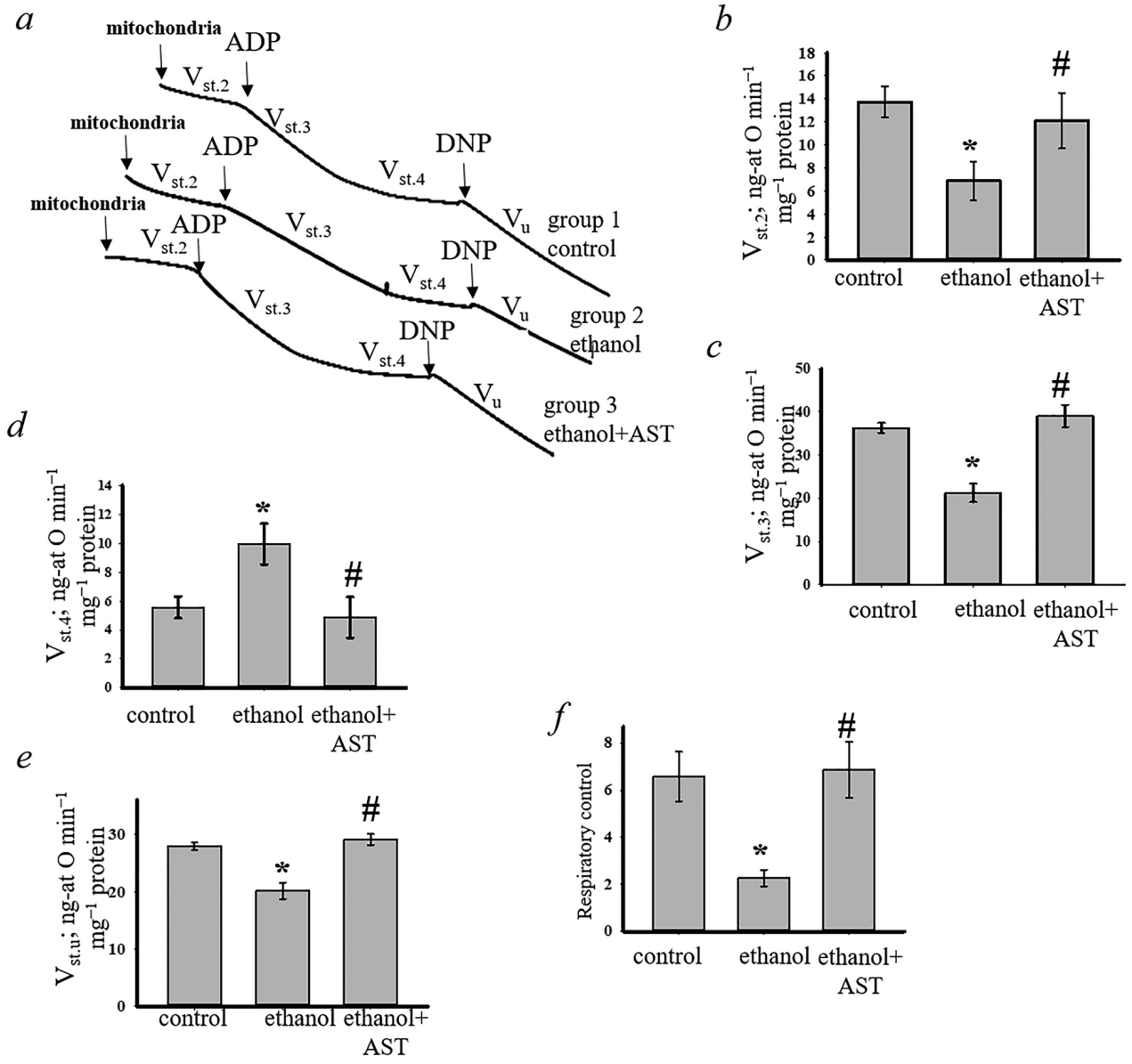

Figure 3. The effect of AST on the respiratory activity of rat cardiac mitochondria during alcohol intoxication. **a** – mitochondrial respiratory activity curves, arrows indicate the addition of ADP (200 μM) and DNP (1 μM); **b** – quantitative analysis of cardiac mitochondrial respiratory activity in State 2 ($V_{st.2}$); **c** – quantitative analysis of cardiac mitochondrial respiratory activity in State 3 ($V_{st.3}$); **d** – quantitative analysis of cardiac mitochondrial respiratory activity in State 4 ($V_{st.4}$); **e** – quantitative analysis of the rate of uncoupled respiration of cardiac mitochondria (V_u). **f** – respiratory control ratio (RCR) values, presented as the ratio of $V_{st.3}$ to $V_{st.4}$. Panel **a** shows the results of a typical experiment, while panels **b**–**f** show the average values of six independent experiments. * $p < 0.05$ – statistically significant difference relative to the control group, # $p < 0.05$ – statistically significant difference relative to the ethanol group.

to alcohol intoxication, the values of $V_{st.2}$ and $V_{st.3}$ decreased by 50% and 41.6%, respectively, compared to the control. Co-administration of AST together with ethanol prevented the alcohol-induced decrease in $V_{st.2}$ and $V_{st.3}$ and the values of these parameters in this group of animals did not differ from the control values. AST also did not change the control value of the mitochondrial oxygen consumption rate in $V_{st.4}$ (Fig. 3d), whereas in the case of alcohol intoxication this parameter increased in the rat heart mitochondria by 78% compared to the control. Figure 3e shows the change in the oxygen consumption rate during uncoupled mitochondrial respiration (V_u). As can be seen from Figure 3e, the V_u value decreased by 27.8% during alcohol intoxication compared to the control. This suggests that under these conditions, electron transport in the electron transport chain (ETC) may be slowed or disrupted (e.g., due to decreased expression of respiratory chain subunits).

The V_u value after AST administration did not differ from the control, despite alcohol consumption by the rats. As shown in Figure 3f, during alcohol intoxication, the RCR value decreased by 2.5 times compared to the control. AST administration prevented the decrease in the RCR value in rat cardiac mitochondria.

Thus, the data obtained indicate that alcohol administration *in vivo* resulted in a decrease in the oxygen consumption rate by mitochondria isolated from rat hearts, reduced RCR, while AST administration together with ethanol prevented the decrease in the mitochondrial oxygen consumption rate and increased the RCR value.

Mitochondrial bioenergetics is known to be realized through the respiratory chain, a system of enzymatic complexes located in the inner mitochondrial membrane. These complexes transfer electrons from donors (e.g. NADH) to the final acceptor (oxygen), releasing energy that is then used for proton translocation across the membrane and subsequent ATP synthesis [33]. As mentioned earlier, chronic alcohol consumption negatively affects the mitochondrial respiration and oxidative phosphorylation system [30]. Thus, the action of ethanol suppresses activity of mitochondrial respiratory complexes, such as cytochrome *c* oxidase (complex IV), reducing both coupled respiration and ATP synthesis, and inducing energy deficiency in cells [34–36]. Since AST is able to positively affect mitochondrial respiration under conditions of alcohol intoxication, in the next stage of the study, we have studied the effect of AST on changes in the content of the main subunits of the mitochondrial respiratory chain complexes during alcohol intoxication (Fig. 4).

Figure 4a shows a Western blot of the studied proteins, and Figure 4b shows a quantitative analysis of changes in the protein content normalized to Tom20. *In vivo* treatment of rats with ethanol reduced the content of the 55 kDa protein subunit of ATP5A complex V by 52.4%, while in the case of ethanol co-administration with AST did not change the subunit level compared to the control. Similar results were observed for the other subunits studied. For example, the content of the 48 kDa UQCRC2 subunit (complex III), 40 kDa MTCO1 subunit (complex IV), 30 kDa SDHB subunit (complex II), and 20 kDa NDUFB8 subunit (complex I) were reduced by after the treatment with ethanol by 50%, 70%, 30%, and 55%, respectively, compared to the control ($p = 0.017, 0.025, 0.010, 0.001$, and 0.001, respectively). However, after the co-administration combined action of ethanol and AST, the subunit levels did not differ from the control. Thus, AST prevents the ethanol-induced decrease in subunit content. This indicates the AST potential to eliminate the negative consequences of alcohol consumption by improving mitochondrial bioenergetic processes.

Cells constantly undergo dynamic processes such as mitochondrial fission and fusion, which are essential for maintaining cellular health by providing energetic adaptation (fusion in response to stress, fission under load), quality control (fission of damaged mitochondria), and maintaining the diversity and stability of the mitochondrial population [37]. In addition, fusion and fission allow mitochondria to meet cellular energy needs in response to environmental stimuli [38, 39]. Mitochondrial fusion often leads to increased oxidative phosphorylation and an increase in mitochondrial membrane potential [40]. Conversely, an increased content of fragmented mitochondria is often associated with a decrease in mitochondrial membrane potential and oxidative phosphorylation, and therefore with a decrease in mitochondrial functioning [40]. Thus, there is evidence confirming the negative impact of alcohol on the balance of mitochondrial dynamics [26, 41]. Therefore, we have investigated the changes in proteins involved in mitochondrial fission (DRP1) and fusion (Mfn2 and OPA1) under our experimental conditions (Fig. 5). Treatment with ethanol caused an increase of the DRP1 level by 43%, while Mfn2 and OPA1 levels decreased by 45% and 43% ($p < 0.01$ in both cases) compared to the control group. Chronic co-administration of AST together with ethanol did not change the protein levels compared to the control group, but not compared to the levels observed in the group of animals treated with ethanol alone (DRP1 levels decreased, while Mfn2 and OPA1 increased). Thus, AST was able to reduce fission of mitochondrial exposed to ethanol, and simultaneously increased their fusion. This leads to a decrease in the number of fragmented mitochondria and an increase in the number of "energized", functional mitochondria. This confirms the protective effect of AST on cardiac mitochondria under conditions of chronic alcohol intoxication.

Mitochondrial fusion and fission maintain mitochondrial function and integrity by exchanging contents and isolating damaged areas. Accumulation of severe mitochondrial damages triggers mitophagy, an autophagic mechanism in which damaged mitochondria are captured and utilized by cellular lysosomes. This process maintains cellular homeostasis and prevents accumulation of dysfunctional mitochondria, which cause oxidative stress and cell death [42]. Therefore, during the next step of this study, changes in the content of proteins involved in mitophagy, such as PINK1 and Parkin, were examined (Fig. 6). Figure 6a,b shows a Western blot stained with the corresponding antibodies at the top. The bottom panel shows the quantitative characteristics of the immunostaining. The figure shows that ethanol exposure decreased the levels of both PINK1 and Parkin by 58% and 41%, respectively, relative to the control. The decrease

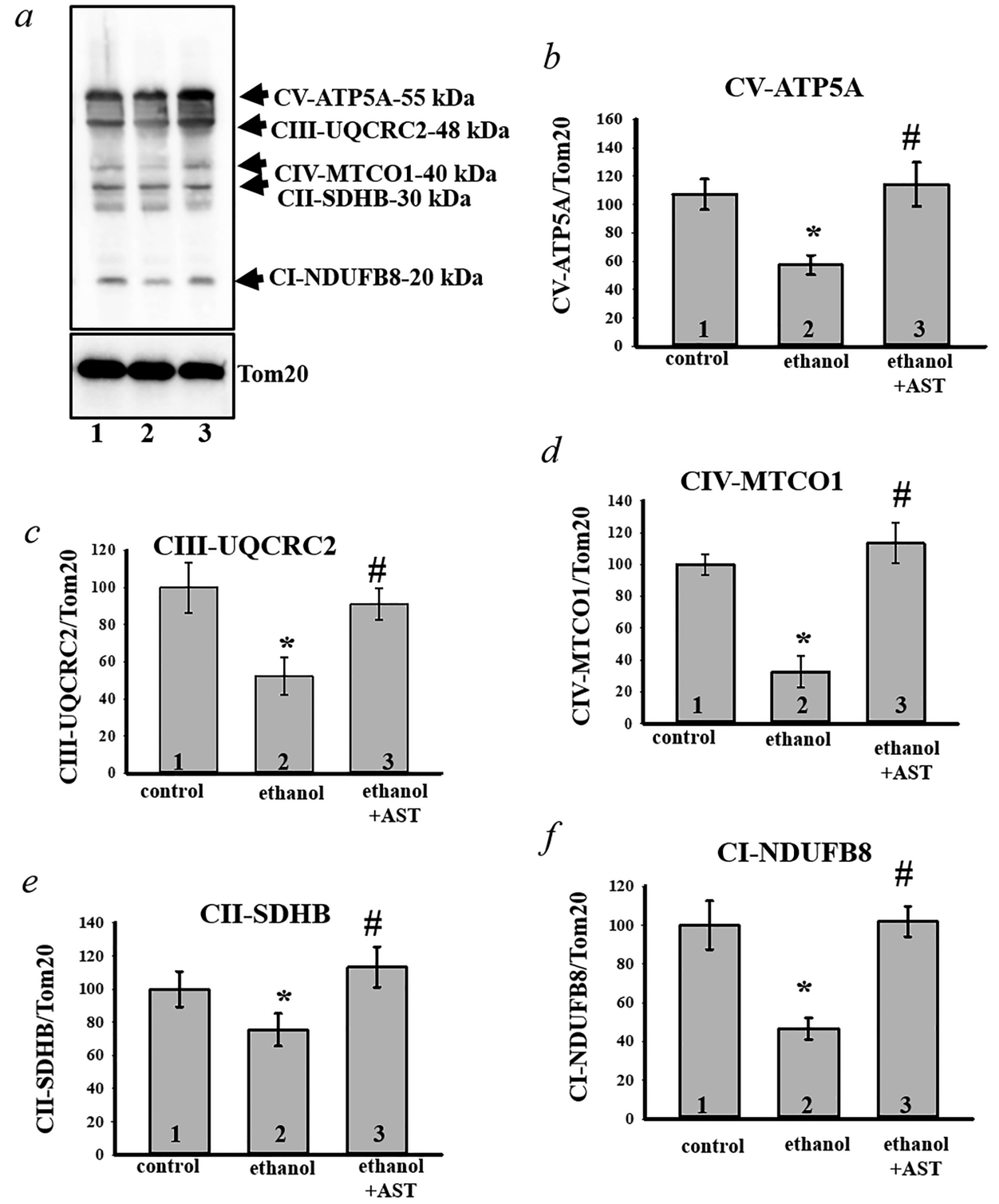

Figure 4. The effect of AST on changes in the content of the main subunits of the mitochondrial respiratory chain complexes during alcohol intoxication. Antibodies to Tom20 were used as a control for protein load. **a** – immunoblots stained with OXPHOS antibodies; **b** – a diagram quantifying the change in the CV-ATP5A protein content, normalized to the Tom20 protein; **c** – a diagram quantifying the change in the CIII-UQCRC2 protein content, normalized to the Tom20 protein; **d** – a graph quantifying the change in CIV-MTCO1 protein content normalized to Tom20; **e** – a graph quantifying the change in CII-SDHB protein content normalized to Tom20; **f** – a graph quantifying the change in CI-NDUFB8 protein content normalized to Tom20. Panel **a** shows the results of a typical experiment, while panels **b**–**f** show the mean values of four independent experiments. * $p < 0.05$ statistically significant difference relative to the control group, # $p < 0.05$ statistically significant difference relative to the ethanol group.

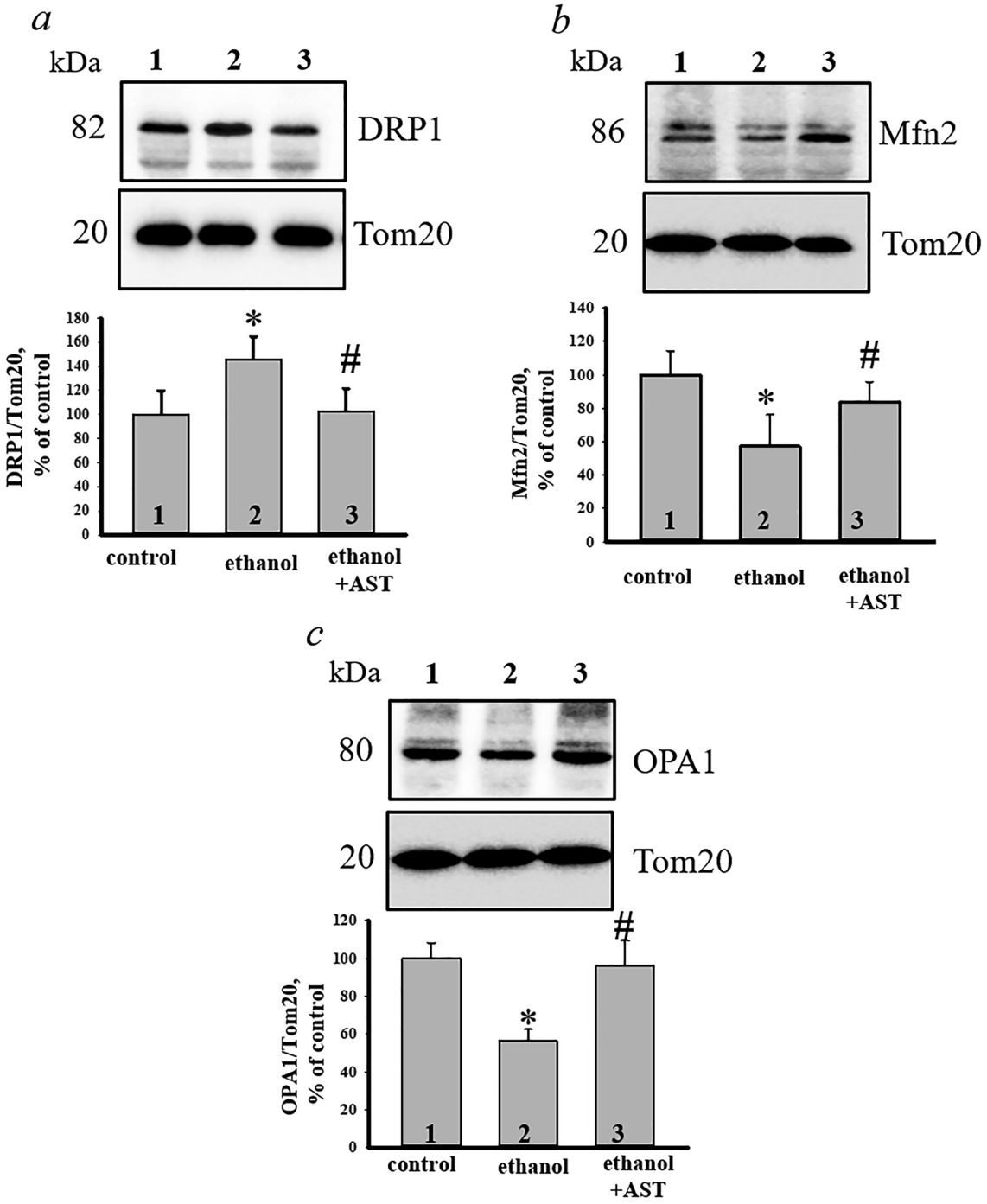

Figure 5. The effect of AST on changes in the content of proteins involved in mitochondrial fission, DRP1 (**a**), and fusion, Mfn2 (**b**) and OPA1 (**c**), during ethanol intoxication. (**a**) The upper part of the figure: immunoblots stained with the corresponding antibodies; the lower part: graphs quantifying changes in protein content normalized to the Tom20 protein. Antibodies to Tom20 were used as a control for protein loading. The immunoblots in the upper part show the results of a typical experiment, while the graphs below show the average values of four independent experiments. * $p < 0.05$: statistically significant difference relative to the control group; # $p < 0.05$: statistically significant difference relative to the ethanol group.

in the levels of these proteins suggests that the mitophagy process was impaired, and damaged mitochondria could accumulate in the cells. In the case of combined action of ethanol and AST, protein levels did not differ from the control but increased relative to the group of animals treated with ethanol alone. AST prevented the ethanol-induced decrease in protein levels. Thus, AST protects mitochondrial respiration and mitochondrial respiratory chain complexes, just as it protects ATPase during chronic alcohol consumption. It prevents degenerative changes in mitochondria, preserves their structure and functionality, and regulates mitochondrial dynamics

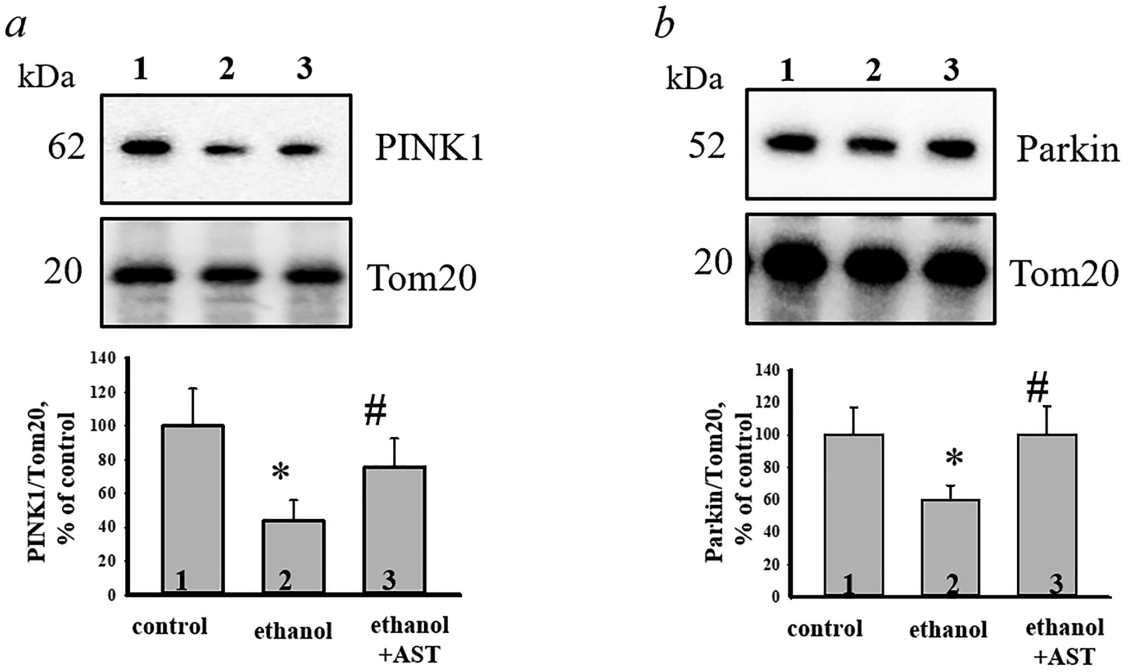

Figure 6. The effect of AST on changes in the content of proteins involved in mitophagy: PINK1 (**a**) and Parkin (**b**) during ethanol intoxication. Antibodies to Tom20 were used as a control for protein loading. Values from three independent experiments are shown. The immunoblots in the upper part show the results of a typical experiment, while the graphs below show the average values of four independent experiments. * $p < 0.05$ significant difference relative to the control group, # $p < 0.05$ significant difference relative to the ethanol group.

and Ca^{2+} homeostasis. These mechanisms reducing oxidative stress and cellular damage, help to restore normal energy metabolism and prevent activation of pro-apoptotic signaling pathways.

AST specifically targets alcohol intoxication without causing imbalances in healthy tissues, making it a promising treatment and prevention option for alcohol-induced mitochondrial dysfunction. It should be noted that we previously observed a similar "hepatoprotective" effect of AST in liver mitochondria [8, 9]. This suggests a complex effect of AST on mitochondria and makes it a promising agent for the treatment of alcoholism-related diseases. Further research is required to determine the precise mechanism(s) of this action, but it can be hypothesized that the protective effect of AST in chronic alcohol intoxication may be mediated through several interconnected mechanisms beyond its classic antioxidant function.

Thus, the AST ability to indirectly reduce oxidative stress by improving mitochondrial respiratory chain function and reducing electron leakage appears important, as demonstrated in our study. Furthermore, a key mechanism is the AST effect on regulatory signaling cascades. We have found that AST increases phosphorylation and, consequently, inactivates GSK-3β kinase; this leads to an increase in the mPTP opening threshold [19]. In addition, AST promotes activation of the CREB transcription factor, which can mediate the expression of genes responsible for cell survival and mitochondrial biogenesis [8]. AST acts as a regulator of mitochondrial permeability, which is an integrative result of its action [8]. We have shown that AST normalizes the content and interaction of key mPTP regulatory proteins, such as Cyclophilin D, ANT, and PiC [3], and modulates the expression of proteins of the TSPO/VDAC/CNPase associated complex [3]. In this study, we have demonstrated that AST influences mitochondrial dynamics, shifting the balance towards organelle fusion, which contributes to increased efficiency of oxidative phosphorylation and stress resistance.

Thus, AST exhibits pleiotropic properties, capable of simultaneously affecting several key nodes of mitochondrial dysfunction.

CONCLUSIONS

In conclusion in should be noted that AST exhibits a pronounced protective effect on mitochondrial respiration and respiratory chain complexes during chronic alcohol consumption. It effectively prevents degenerative changes in mitochondria, maintains their structural integrity and functionality, and regulates mitochondrial dynamics and normalizes calcium levels, thus promoting reduction of oxidative stress and cellular damage. This demonstrates the potential of AST as a promising treatment and prevention tool for alcohol-induced mitochondrial dysfunction and opens wide prospects for its use in the treatment of diseases associated with alcoholism.

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COMPLIANCE WITH ETHICAL STANDARDS

The study was conducted in accordance with generally accepted international standards for the treatment of animals (Directive 2010/63/EU of the European Parliament and of the Council of the European Union on the protection of animals used for scientific purposes of September 22, 2010), as well as the Regulation on Research on Experimental Animals (Order of the Ministry of Health of the Russian Federation of August 12, 1997, no. 755), and was approved by the Biological Safety and Ethics Committee of the Institute of Theoretical and Experimental Biophysics of the Russian Academy of Sciences (Protocol no. 07/2025 of March 3, 2025).

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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АСТАКСАНТИН ЗАЩИЩАЕТ МИТОХОНДРИИ СЕРДЦА ОТ ПОВРЕЖДЕНИЙ, ВЫЗВАННЫХ ХРОНИЧЕСКОЙ АЛКОГОЛЬНОЙ ИНТОКСИКАЦИЕЙ

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Получены результаты, показывающие кардиопротекторное действие природного антиоксиданта астаксантина (АСТ) на митохондрии сердца крыс при хронической алкогольной интоксикации. В частности, АСТ восстанавливал дыхательную активность и Ca^{2+}-ёмкость митохондрий сердца при хронической алкогольной интоксикации, оказывал положительное влияние на баланс функционально-значимых процессов деления/слияния митохондрий, а также митофагии. Кроме того, АСТ предотвращал морфологические повреждения ткани сердца, вызванные алкоголем. В целом, результаты показывают, что АСТ способствует нормализации работы митохондрий сердца, защищая их от дегенеративных изменений, вызванных алкогольной интоксикацией, и улучшая энергетический метаболизм сердечной ткани. Таким образом, астаксантин помогает компенсировать повреждения митохондрий сердца, вызванные хроническим приёмом алкоголя, восстанавливая их функциональную активность и устойчивость к стрессу.

Полный текст статьи на русском языке доступен на сайте журнала (http://pbmc.ibmc.msk.ru).

Ключевые слова: митохондриальная дисфункция; хроническая алкогольная интоксикация; астаксантин; митохондрии сердца; митофагия; деление/слияние митохондрий

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