International Journal of Biochemistry and Cell Biology 89 (2017) 125–135

Contents lists available at ScienceDirect

International Journal of Biochemistry and Cell Biology

journal homepage: www.elsevier.com/locate/biocel

Review article

Etiology of alcoholic cardiomyopathy: Mitochondria, oxidative stress and apoptosis

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ARTICLE INFO

Keywords:
Reactive oxygen species
Respiratory chain
Ethanol
Heart
Caspase

ABSTRACT

Putative mechanisms leading to the development of alcoholic cardiomyopathy (ACM) include the interrelated cellular processes of mitochondria metabolism, oxidative stress and apoptosis. As mitochondria fuel the constant energy demands of this continually contracting tissue, it is not surprising that alcohol-induced molecular changes in this organelle contribute to cardiac dysfunction and ACM. As the causal relationship of these processes with ACM has already been established, the primary objective of this review is to provide an update of the experimental findings to more completely understand the aforementioned mechanisms. Accordingly, recent data indicate that alcohol impairs mitochondria function assessed by membrane potential and respiratory chain activity. Indictors of oxidative stress including superoxide dismutase, glutathione metabolites and malondialdehyde are also adversely affected by alcohol oftentimes in a sex-dependent manner. Additionally, myocardial apoptosis is increased based on assessment of TUNEL staining and caspase activity. Recent work has also emerged linking alcohol-induced oxidative stress with apoptosis providing new insight on the codependence of these interrelated mechanisms in ACM. Attention is also given to methodological differences including the dose of alcohol, experimental model system and the use of males versus females to highlight inconsistencies and areas that would benefit from establishment of a consistent model.

1. Introduction

Alcoholic cardiomyopathy (ACM) is a consequence of excessive alcohol intake for a prolonged period of time and is oftentimes accompanied by impaired cardiac contractility and function (e.g., blood pressure, cardiac output, etc.) (Fernández-Solà, 2015). As no definitive diagnostic criteria have been established, ACM is typically diagnosed based on exclusion of other contributing factors in patients with dilated cardiomyopathy and a history of excessive alcohol use. In developed countries where per capita alcohol consumption is high, ACM represents a leading cause of non-ischemic dilated cardiomyopathy (Graves, 1995). The prevalence of ACM has been reported to represent between 4 − 47% of all cases of dilated cardiomyopathy and this high variability appears largely dependent on the specific inclusion criteria (i.e., cumulative alcohol intake, sex, geographic location) used for its classification (Kasper et al., 1994; Haissaguerre et al., 1989; Gavazzi et al., 2000; Fauchier et al., 2000; Prazak et al., 1996). While not all those classified with alcohol use disorder (AUD) develop the disease, its contribution to mortality associated with alcohol intake is unequivocal. Therefore, determining the cellular and molecular factors leading to the onset and progression of ACM is central to developing effective treatment strategies.

ACM is a multifactorial disease and defects in mitochondrial function, oxidative stress and apoptosis appear fundamental to its etiology. The aim of this article is to provide an unbiased review of the new and important discoveries related to the role and association between

Abbreviations: ACM, alcoholic cardiomyopathy; ALDH, aldehyde dehydrogenase; ADH, alcohol dehydrogenase; PKC-β, protein kinase C (PKC)-beta; TCA cycle, tricarboxylic acid; ETC, electron transport chain; RCI, mitochondrial respiratory control index/ratio; FAD+, flavin adenine dinucleotide; CoQ, coenzyme Q; COX IV, cytochrome c oxidase; AMPK, AMP-activated protein kinase; ANT1, adenine nucleotide translocator 1; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; UCP2, uncoupling protein-2; ERRα, estrogen related receptor alpha; mtDNA, mitochondria DNA; ROS, reactive oxygen species; $O_2\cdot^-$, superoxide anion radical; ·OH, hydroxyl radical; H_2O_2, hydrogen peroxide; $^1O_2$, singlet oxygen; GSH, glutathione; SOD, superoxide dismutase; E2, estrogen; IGF-I, insulin like growth factor – I; CYP2E1, cytochrome P450 2E1; Cu/ZnSOD, SOD1, copper/zinc-containing SOD; MnSOD, SOD2, manganese SOD; ECSOD, SOD3, extracellular superoxide dismutase; kcal, kilocalories; NaHS, sodium hydrosulfide; H_2S, hydrogen sulfide; GSH, glutathione; GPx, glutathione peroxidase; GSSG, glutathione disulfide; SPH, sardinelle heads; GST, glutathione S-transferase; MDA, malondialdehyde; TBARS, thiobarbituric acid reactive substances; 4-HNE, 4-hydroxynonenal; Hsp, heat shock proteins; HSF1, heat shock factor 1; HO-1, heme oxygenase-1; dP/dt, max maximal rise of (ventricular) pressure over time; ± dL/dt, maximal velocity of shortening/relengthening; TR90, time to 90% of relengthening; AIF, apoptosis inducing factor; TNF-α, tumor necrosis factor alpha; FasL, fas ligand; AT1, angiotensin II type I; RGS6, regulator of G protein signaling 6 gene; LV, left ventricular; TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labeling; GR, glutathione reductase

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http://dx.doi.org/10.1016/j.biocel.2017.06.009
Received 16 February 2017; Received in revised form 7 June 2017; Accepted 8 June 2017
Available online 09 June 2017
1357-2725/

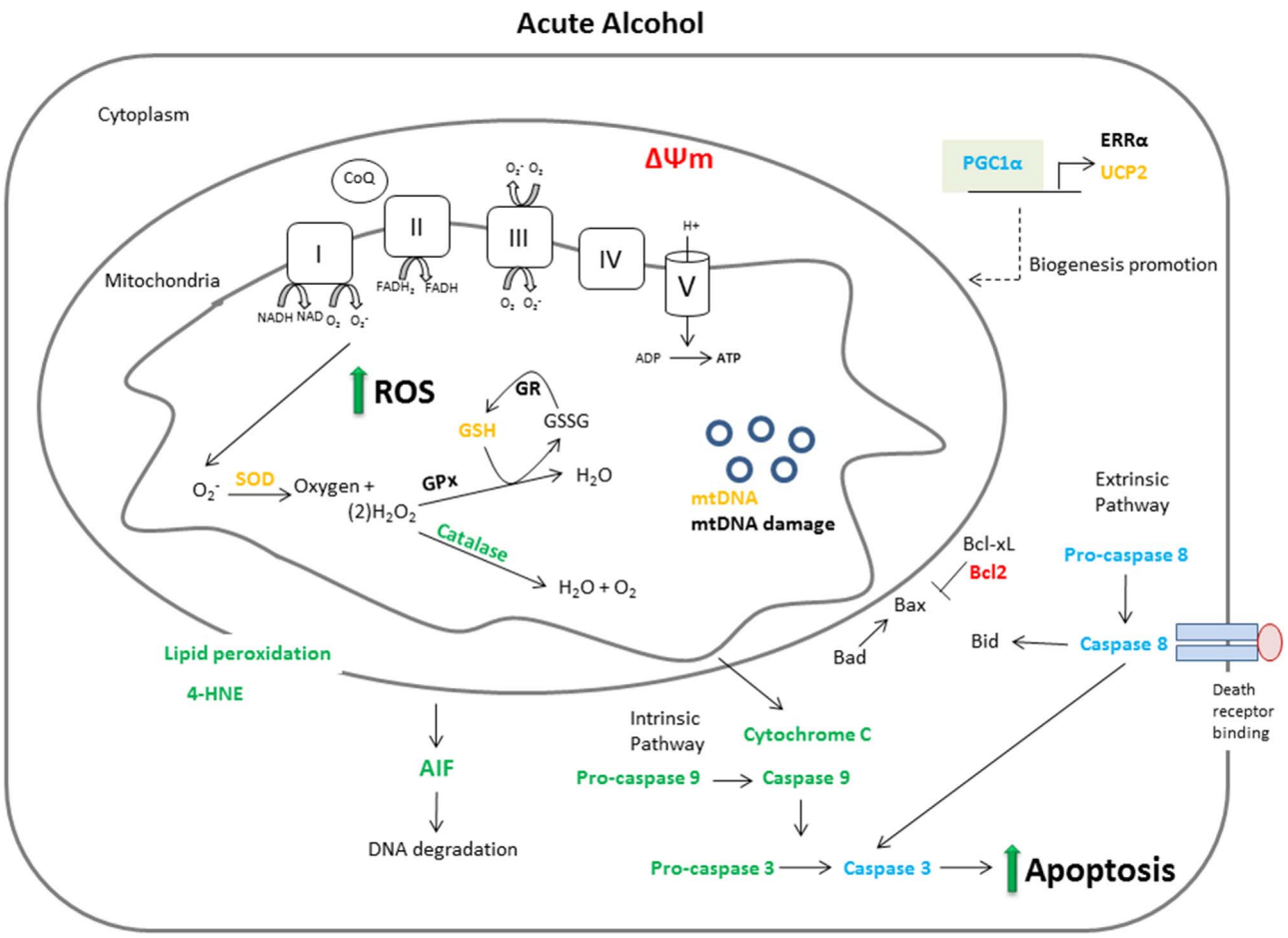

Fig. 1. Overview of the impact of acute alcohol intoxication on mitochondrial mediated aspects of ACM. Those factors listed in red were decreased by alcohol, those in green were increased and those in blue were unchanged. Orange print indicates that measured changes were inconsistent between studies and black signifies that no measurement was made in the included literature between 2010 and 2017. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

mitochondria, oxidative stress and apoptosis in the development of ACM. To achieve this objective and provide a concise presentation, only research published between 2010 and the first half of 2017 (when this review was written) will be discussed aside from the limited inclusion of seminal articles that provide the context necessary for the understanding of the current findings. As such, the reader is directed to other high quality reviews for further historical perspective (Piano and Phillips, 2014; Guzzo-Merello et al., 2014; Laurent and Edwards, 2014; Walker et al., 2013). The scope of this review is therefore limited to work published since 2010 that included the measurement of mitochondria function, oxidative stress and/or apoptosis subsequent to either acute or chronic alcohol treatment in vitro, in animal models or in humans. Additionally, effort was made to identify methodological differences, including those related to alcohol dose and duration as well as the sex of the subject as these represent an important source of variability that likely contributed to observed differences in experimental outcomes. Finally, to ensure an unbiased review of the literature, we have included all well-designed studies whether or not their findings support the prevailing hypothesis in an area. Figs. 1 and 2 which summarize the response of heart and cardiomyocytes to acute and chronic exposure to alcohol, respectively, are presented to provide a visual framework for which the subsequent literature review.

2. Mitochondria

2.1. Structure and function

The impact of alcohol on heart mitochondria structure was established by early work that demonstrated alcohol produced mitochondria enlargement and degeneration of inner mitochondria membrane folds (Tsiplenkova et al., 1986; Hibbs et al., 2016). These findings were recently extended to show that chronic alcohol consumption decreased mitochondrial number, but not size (Jing et al., 2011), and increased mitochondria fragmentation (Zhang et al., 2010).

2.1.1. Membrane potential

Consistent with the reported structural alterations, alcohol also impaired mitochondrial function. Mitochondrial membrane potential or more specifically early membrane depolarization has been used as an indicator of mitochondrial dysfunction (Reers et al., 1995). When cardiomyocytes were cultured with alcohol (100 mM, 6 days or 50–200 mM, 24 h) the membrane potential was decreased and the percentage of depolarized mitochondria was increased (Laurent et al., 2014; Wang et al., 2016; Wang et al., 2015). Acute alcohol intoxication (1 or 3 day, 3 g/kg) in male mice led to a similar decrement in membrane potential (Guo and Ren, 2010; Ma et al., 2010). The generation of alcohol metabolites may have contributed to the alcohol mediated mitochondrial changes as the decrease in membrane potential was greater in mice lacking aldehyde dehydrogenase (ALDH) or alcohol dehydrogenase (ADH) than in wild-type littermates (Guo and Ren, 2010; Ma et al., 2010). Dysregulation of the SHC (SRC homology 2 containing) (p66Shc)/Pin1 pathway was also implicated in the alcohol-induced change in mitochondrial membrane potential. Specifically, Pin1 overexpression exacerbated the alcohol-induced decrease in mitochondrial membrane potential, whereas mitochondrial dysfunction was prevented by the knockdown of Pin1 or blockade of either p66Shc