Available online at www.sciencedirect.com

Metabolism

www.metabolismjournal.com

Endoplasmic Reticulum Stress Response in Non-alcoholic Steatohepatitis: The Possible Role of Physical Exercise

Emanuel Passos[a,b], *António Ascensão*[b], *Maria João Martins*[a], *José Magalhães*[b,*]

[a] *Department of Biochemistry, Faculty of Medicine and Instituto de Investigação e Inovação em Saúde, University of Porto, Porto, Portugal*
[b] *Research Centre in Physical Activity, Health and Leisure, Faculty of Sport, University of Porto, Porto, Portugal*

ARTICLE INFO

Article history:
Received 1 July 2014
Accepted 17 February 2015

Keywords:
Non-alcoholic steatohepatitis
Endoplasmic reticulum stress
Chemical chaperones
Physical exercise
Cardiovascular disease

ABSTRACT

Sedentary lifestyle coupled with excessive consumption of high caloric food has been related to the epidemic increase of non-alcoholic fatty liver disease, which can progress from simple steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis and, eventually, may culminate in hepatocellular carcinoma. Although the precise mechanisms underlying the progression of NASH are not completely understood, endoplasmic reticulum (ER) dysfunction seems to play a key role in the process. Hepatic ER stress has been associated to hepatic steatosis, insulin resistance, inflammation, oxidative stress and hepatocyte death, contributing to liver dysfunction. Physical exercise seems to be the most effective preventive and therapeutic non-pharmacological strategy to mitigate several features related to NASH, possibly targeting most of the referred mechanisms associated with the pathophysiology of ER-related NASH. Nevertheless, little is known about the impact of physical exercise on NASH-related ER stress. In this review, we will discuss the ER stress associated to NASH conditions and highlight the possible benefits of physical exercise in the attenuation and/or reversion of NASH-related ER stress.

Abbreviations: NAFLD, non-alcoholic fatty liver disease; T2DM, type 2 diabetes mellitus; NASH, non-alcoholic steatohepatitis; ER, endoplasmic reticulum; ERAD, ER-associated degradation; UPR, unfolded protein response; PERK, protein kinase RNA-activated (PKR)-like ER kinase; IRE1, inositol requiring enzyme 1; ATF-6, activating transcription factor 6; BiP, binding immunoglobulin protein; eIF2α, eukaryotic translation initiation factor-2 α; ATF-4, activating transcription factor 4; ERO1, endoplasmic reticulum oxireductin 1; Nrf2, nuclear erythroid 2 p45-related factor; GADD34, growth arrest and DNA damage-inducible protein; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; S1P, site-1 protease; S2P, site-2 protease; XBP1, X-box binding protein-1; SREBP, sterol regulatory element-binding protein; SERCA, sarco/ER pump calcium ATPase; ROS, reactive oxygen species; IκB, inhibitor of NF-κB; IKK, IκB kinase; JNK, c-Jun N-terminal kinase; IL-1β, interleukin-1 beta; IL-6, interleukin-6; TNFα, tumor-necrosis factor α; TRAF2, TNF-receptor-associated factor 2; CREBH, cyclic AMP response element-binding protein H; GRP94, glucose related protein 94; IRS1, insulin receptor substrate 1; IRS2, insulin receptor substrate 2; PI3K, phosphoinositide 3-kinase; PI(4,5)P2, phosphatidylinositol 4,5-bisphosphate; PI(3,4,5)P3, phosphatidylinositol (3,4,5)-trisphosphate; ASK1, apoptosis signaling-regulating kinase 1; CHOP, C/EBP homologous protein; PTP1B, protein tyrosine phosphatase 1B; Keap1, Kelch ECH associating protein 1; PDI, protein disulfide isomerase; FAD, flavin adenine dinucleotide; MAM, mitochondrial-associated ER membrane; HFD, high-fat diet; TLR, Toll-like receptor; PBA, 4-phenyl butyric acid; TUDCA, taurine-conjugated ursodeoxycholic acid.

* *Corresponding author at:* Research Centre in Physical Activity, Health and Leisure, Faculty of Sport, University of Porto, Rua Dr. Plácido Costa, 91, 4200-450 Porto, Portugal. Tel.: +351 225074774; fax: +351 225500689.
E-mail address: jmaga@fade.up.pt (J. Magalhães).

http://dx.doi.org/10.1016/j.metabol.2015.02.003
0026-0495/

1. Introduction

Sedentary lifestyle coupled with excessive consumption of high-caloric diets has been linked to the manifestation of metabolism-related pathological signs, including those characterizing non-alcoholic fatty liver disease (NAFLD) [1–3]. The relevant role of liver in systemic metabolic regulation argues for the association of NAFLD and metabolic dysfunction [3,4]. NAFLD represents the hepatic manifestation of the metabolic syndrome, which includes central obesity, hypertension, glucose intolerance and dyslipidemia, in addition to pro-inflammatory and pro-trombotic states, and comprises an increased risk for type 2 diabetes mellitus (T2DM) and atherosclerotic cardiovascular events [4–8]. In this scenario, elevated levels of circulating free fatty acids, and their consequent uptake by the liver, appears to play a major role in the development and progression of hepatic steatosis and insulin resistance [8–11]. In fact, aberrant hepatic lipid droplet accumulation has been associated with NAFLD that can progress from steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis and, eventually, to hepatocellular carcinoma [2,8,12,13]. While hepatic steatosis, insulin resistance and oxidative stress characterize both NAFLD and NASH, NASH, in particular, is also associated with increased production of inflammatory mediators, increased apoptotic signaling and fibrosis in the liver [2,12]. Mitochondrial dysfunction seems to be involved in the onset and/or progression of NASH [14–16]. Additionally, prolonged endoplasmic reticulum (ER) dysfunction is also implicated in the regulation of liver lipid metabolism as well as in the development of steatosis and NASH [13,17–23].

ER has an important role as a sensor of cellular stress [24–26]. Under pathological and/or stressful conditions, in which the demand of protein synthesis is increased (e.g. NASH), an imbalance between the load of needed protein-folding and the response-related capability of the ER can lead to the accumulation of immature and/or misfolded proteins within the ER lumen [22,25,26]. This results in compromised functionality of this organelle and decreased mitochondrial function, ultimately leading to liver dysfunction [19,24]. Under both unmitigated ER and mitochondrial dysfunctions, restoration of ER homeostasis fails and the activation of the apoptotic signaling occurs [19,27]. Therefore, critical steps of ER dysfunction-related signaling pathways could be interesting therapeutic targets in NASH [28].

Several epidemiological and observational studies suggest that physical inactivity associates with obesity, inflammation, insulin resistance, T2DM and NASH [2,21,22,29]. On the other hand, interventional studies demonstrate that regular physical exercise has the potential to modulate several features related to the metabolic syndrome and NASH. In particular, it decreases both oxidative stress and inflammation, improves insulin sensitivity and reverses mitochondrial and ER dysfunctions [30–38].

In this review, we briefly discuss the ER dysfunction-induced NASH and the related inflammation, insulin resistance, oxidative stress and apoptotic signaling pathways. Thereafter, besides a brief presentation on exogenous chemical chaperones as relevant pharmacological interventions, we present and discuss detailed data that highlight the benefits of chronic regular physical exercise as a non-pharmacological therapeutic tool in the prevention, attenuation and/or reversion of NASH-related ER dysfunction and its associated deleterious consequences.

2. ER stress-induced unfolded protein response

Besides being a critical site for intracellular storage of calcium in the cell, the ER is also a vast dynamic and tubular network responsible for the synthesis, maturation, quality control and trafficking of a wide range of proteins. Therefore, the ability of the ER to adapt and manage adverse conditions is vital for the cell [21,26]. Only correctly folded proteins exit the ER to their final destination. So, unfolded and misfolded proteins are either retained in the ER lumen, with the molecular chaperones, to be correctly refolded or directed toward proteasomal degradation, in a process called ER-associated degradation (ERAD) [39]. Under pathological and/or stressful conditions, such as NASH, and due to the high demand for protein synthesis, folding and/or repair, decreased efficiency in the ER protein-folding, quality control and/or trafficking machinery is observed, most particularly in highly metabolic tissues (like the liver). This leads to a cellular perturbation termed *ER stress*, which results in the accumulation of unfolded and/or misfolded proteins [20–22,26,40]. In an attempt to restore homeostasis, ER elicits an elaborated adaptive response collectively known as the *unfolded protein response* (UPR) [26,40]. The UPR is characterized by the activation of three distinct signal transduction pathways mediated by three transmembrane sensors: protein kinase RNA-activated (PKR)-like ER kinase (PERK), inositol requiring enzyme (IRE) 1 and activating transcription factor (ATF)-6 [19,26]. In coordination, the three branches of the UPR regulate the transcription of various genes involved in the expansion of ER, the decrease of protein synthesis and the increase of protein folding capability and the degradation of terminally unfolded and misfolded proteins within ER [19,26,40].

In the absence of ER stress, the three transmembrane UPR sensors are maintained in an inactive state through binding to the ER chaperone binding immunoglobulin protein (BiP) [24]. However, when the protein load in the ER overcomes the ER folding or quality control capability, BiP detaches activating the UPR. This event results in the oligomerization and activation of both PERK and IRE1 through trans-autophosphorylation while ATF-6 translocates to the Golgi complex [26].

When activated, PERK phosphorylates the eukaryotic translation initiation factor-2 (eIF2)α, leading to immediate transient attenuation of protein synthesis, and, subsequently, prevents continued influx of newly synthesized polypeptides into the ER, thus reducing the ER workload [21,22,24,39]. However, considering that some level of protein-synthesis should be maintained, this pathway selectively induces the translation of ATF-4 and the expression of genes involved in ER redox control [endoplasmic reticulum oxireductin 1 (ERO1) and nuclear erythroid 2 p45-related factor (Nrf2)] [24,41,42]. Additionally, the PERK pathway is also responsible for cell recovery from protein synthesis shut-off through dephosphorylation of eIF2α [by growth arrest and DNA damage-inducible protein (GADD34)].