Causal role of oxidative stress in unfolded protein response development in the hyperthyroid state

Luis A. Videla, Virginia Fernández, Pamela Cornejo, Romina Vargas, Juan Carrasco, Javier Fernández, Nelson Varela

www.elsevier.com

PII: S0891-5849(15)00569-9
DOI: http://dx.doi.org/10.1016/j.freeradbiomed.2015.09.004
Reference: FRB12557

To appear in: *Free Radical Biology and Medicine*

Received date: 16 April 2015
Revised date: 9 September 2015
Accepted date: 11 September 2015

Cite this article as: Luis A. Videla, Virginia Fernández, Pamela Cornejo, Romina Vargas, Juan Carrasco, Javier Fernández and Nelson Varela, Causal role of oxidative stress in unfolded protein response development in the hyperthyroid state, *Free Radical Biology and Medicine,* http://dx.doi.org/10.1016/j.freeradbiomed.2015.09.004

Causal role of oxidative stress in unfolded protein response development in the hyperthyroid state

Luis A. Videla[a,*], Virginia Fernández[a], Pamela Cornejo[b], Romina Vargas[a], Juan Carrasco[a], Javier Fernández[a], Nelson Varela[a,c]

[a]Molecular and Clinical Pharmacology Program, Institute of Biomedical Sciences, Faculty of Medicine, and University of Chile, Santiago-7, Chile

[b]School of Medical Technology, Faculty of Health and Odontology, Diego Portales University, Santiago, Chile

[c]Department of Medical Technology, Faculty of Medicine, University of Chile, Santiago-7, Chile

*Corresponding author.

E-mail address: lvidela@med.uchile.cl (L.A. Videla).

Abstract

L-3,3′,5-Triiodothyronine (T_3)-induced liver oxidative stress underlies significant protein oxidation, which may trigger the unfolded protein response (UPR). Administration of daily doses of 0.1 mg T_3 for three consecutive days significantly increased the rectal temperature of rats and liver O_2 consumption rate, with higher protein carbonyl and 8-isoprostane levels, glutathione depletion, and absence of morphological changes in liver parenchyma. Concomitantly, liver protein kinase RNA-like endoplasmic reticulum (ER) kinase and eukaryotic translation initiator factor 2α were phosphorylated in T_3-treated rats compared to controls, with increased protein levels of binding immunoglobulin protein and activating transcription factor 4. In addition, higher mRNA levels of C/EBP homologous protein, growth arrest and DNA damage 34, protein disulfide isomerase, and ER oxidoreductin 1α were observed, changes that were suppressed by *N*-acetylcysteine (0.5 g/kg) given before each dose of T_3. In conclusion, T_3-induced liver oxidative stress involving higher protein oxidation status has a causal role in UPR development, a response that is aimed to alleviate ER stress and promote cell survival.

Keywords: Thyroid hormone calorigenesis; Liver oxidative stress; Protein oxidation; Unfolded protein response; *N*-acetylcysteine; Free radicals

Ischemia and reperfusion (IR) of the liver lead to severe injury (IRI), a feature observed in liver transplantation and liver resection that is associated with oxygen and nutrient deprivation occurring during the procedure in the former case and with vascular occlusion to prevent hemorrhage in the latter case [1,2]. The mechanisms underlying liver IRI gathered in experimental models led to the development of numerous surgical and pharmacological protective strategies; however, few have reached clinical practice [1,2]. Development of an acute, nonlethal burst of oxidative stress constitutes a major pharmacological liver preconditioning (PC) strategy [3,4], which includes the administration of thyroid hormone (L-3,3′,5-triiodothyronine; T_3) before an IR protocol [5], as evidenced by the reestablishment of liver injury after the administration of the antioxidant *N*-acetylcysteine (NAC) before T_3 [6].

T_3 is considered a hormetic agent that triggers biologically beneficial effects in the liver in the low-dose range, leading to cell proliferation and the induction of proteins affording cellular protection, namely, antioxidant, antiapoptotic, and acute-phase proteins [7]; phase II detoxification enzymes; and phase III transporters [8]; and downregulation of the mRNA and protein expression of cytokines and adhesion molecules related to liver inflammation [9]. Accordingly, liver PC is confronted with a major energy requirement to cope with ATP demands for operation of most of the PC mechanisms outlined above, plus those for repair and resynthesis of altered