Free Radical Biology and Medicine ∎ (∎∎∎∎) ∎∎∎–∎∎∎

Contents lists available at ScienceDirect

Free Radical Biology and Medicine

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

Review Article

Nutrient overload, lipid peroxidation and pancreatic beta cell function

Shlomo Sasson

Institute for Drug Research, Section of Pharmacology, Diabetes Research Unit, Hebrew University Faculty of Medicine, Jerusalem 9112001, Israel

ARTICLE INFO

Article history:
Received 14 August 2016
Accepted 2 September 2016

Keywords:
4-Hydroxynonenal
Beta cells
Diabetes
Lipid peroxidation
Lipohormesis
Lipotoxicity

ABSTRACT

Since the landmark discovery of α,β-unsaturated 4-hydroxyalkenals by Esterbauer and colleagues most studies have addressed the consequences of the tendency of these lipid peroxidation products to form covalent adducts with macromolecules and modify cellular functions. Many studies describe detrimental and cytotoxic effects of 4-hydroxy-2*E*-nonenal (4-HNE) in myriad tissues and organs and many pathologies. Other studies similarly assigned unfavorable effects to 4-hydroxy-*2E*-hexenal (4-HHE) and 4-hydroxy-2E,6Z-dodecadienal (4-HDDE). Nutrient overload (e.g., hyperglycemia, hyperlipidemia) modifies lipid metabolism in cells and promotes lipid peroxidation and the generation of α,β-unsaturated 4-hydroxyalkenals. Advances glycation- and lipoxidation end products (AGEs and ALEs) have been associated with the development of insulin resistance and pancreatic beta cell dysfunction and the etiology of type 2 diabetes and its peripheral complications. Less acknowledged are genuine signaling properties of 4-hydroxyalkenals in hormetic processes that provide defense against the consequences of nutrient overload. This review addresses recent findings on such lipohormetic mechanisms that are associated with lipid peroxidation in pancreatic beta cells.

This article is part of a Special Issue entitled SI: LIPID OXIDATION PRODUCTS, edited by Giuseppe Poli.

Contents

1. Introduction . . . 2
2. PUFA metabolites in beta cells . . . 3
3. Phospholipase A2 in beta cells . . . 3
4. Enzymatic PUFA metabolites and beta cells . . . 3
5. Non-enzymatic PUFA metabolites and beta cells - lipid peroxidation . . . 4
6. Clearance of 4-hydroxyalkenals . . . 4
7. Cellular levels and functions of 4-HNE . . . 4
8. Signaling properties of 4-HNE . . . 5
9. Hormetic and detrimental effects of 4-HNE in beta cells . . . 5
10. Summary . . . 6
Conflicts of interests . . . 6
Acknowledgments . . . 6
References . . . 6

1. Introduction . . . 2
2. PUFA metabolites in beta cells . . . 3
3. Phospholipase A2 in beta cells . . . 3

Abbreviations: 4-HDDE, 4-Hydroxy-2*E*,6*Z*-dodecadienal; 4-HHE, 4-Hydroxyl-*2E*-hexenal, 4-HNE, 4-Hydroxy-2*E*-nonenal; AGE, Advanced glycation end products; ALE, Advanced lipoxidation end products; AR, aldose reductase; COX, Cyclooxygenase; EET, Epoxyeicosatrienoic acid; ER, Endoplasmic reticulum; FALDH, Fatty aldehyde dehydrogenase; GPx, Glutathione peroxidase; GSH, Glutathione; GSIS, Glucose-stimulated insulin secretion; GST, Glutathione-S-transferase; HETE, Hydroxyeicosatetraenoic acid; HpETE, Hydroperoxyeicosatetraenoic acid; HpODE, Hydroperoxyoctadecadienoic acid; Keap1, Kelch-like ECH-associated protein; LT, Leukotriene; LO, Lipoxygenase; MUFA, Monounsaturated fatty acids; Nrf2, Nuclear factor (erythroid-derived 2)-like 2; PG, prostaglandin; PKC, Protein kinase C; PDGFR, Platelet-derived growth factor receptor; PLA2, Phospholipase A2; PPARδ, Peroxisome proliferator-activated receptor-δ; PUFA, Polyunsaturated fatty acids; ROS, Reactive oxygen species; SFA, Saturated fatty acids; T2DM, Type 2 diabetes mellitus; TX, Thromboxane

E-mail address: shlomo.sasson@mail.huji.ac.il

http://dx.doi.org/10.1016/j.freeradbiomed.2016.09.003
0891-5849/

Please cite this article as: S. Sasson, Nutrient overload, lipid peroxidation and pancreatic beta cell function, Free Radic. Biol. Med. (2016), http://dx.doi.org/10.1016/j.freeradbiomed.2016.09.003

4. Enzymatic PUFA metabolites and beta cells . . . 3
5. Non-enzymatic PUFA metabolites and beta cells - lipid peroxidation . . . 4
6. Clearance of 4-hydroxyalkenals . . . 4
7. Cellular levels and functions of 4-HNE . . . 4
8. Signaling properties of 4-HNE . . . 5
9. Hormetic and detrimental effects of 4-HNE in beta cells . . . 5
10. Summary . . . 6
Conflicts of interests . . . 6
Acknowledgments . . . 6
References . . . 6

1. Introduction

Type 2 diabetes mellitus (T2DM) is a progressive disease, which is characterized by glucose intolerance, peripheral insulin resistance, beta cell dysfunction and related end-organ damage and complications [1]. These features of the disease are interwoven in a complex crosstalk network among insulin secreting beta cells and peripheral insulin sensitive tissues. This metabolic regulatory network is responsive to and is modified by nutrient overload challenges, particularly hyperglycemia and hyperlipidemia. Many mediators that are involved in the etiology of T2DM have been identified, including excessive production of reactive oxygen species (ROS), altered mitochondrial function, impaired insulin signaling, and increased levels of AGEs and ALEs [2]. Major cellular dysfunctions found in beta cells, skeletal muscles, adipose tissue, liver, vascular endothelial cells and others include disturbed ER homeostasis (ER stress), autophagy, cell senescence and apoptosis [3–9]. Yet, the progression of T2DM is slow and not all patients diagnosed as pre-diabetics progress to the overt phase, while not all diabetic patients exhibit severe peripheral complications. Evidently, cells and tissues have evolved adaptive mechanisms to protect against detrimental effects of nutrient overload. A well-characterized example is the hormetic response ROS evokes by modifying Keap1 (Kelch-like ECH-associated protein), the negative modulator of Nrf2 [Nuclear factor (erythroid-derived 2)-like 2], and releasing the latter to translocate to the nucleus and induce transcription of antioxidant genes that neutralize ROS and reduce the burden of oxidative stress [10–12].

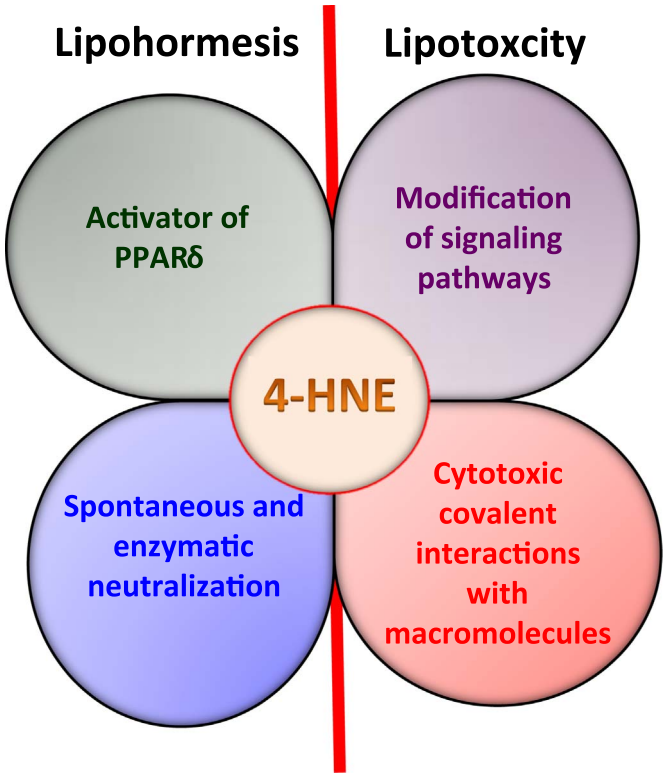

Fig. 1. Major lipohormetic and lipotoxic routes of 4-HNE interactions in beta cells.

Lipohormesis describes mechanisms by which free fatty acids and other lipids evoke protective responses in cells [13,14]. For instance, it has been shown that monounsaturated fatty acids (MUFA) protect cells against cytotoxic effects of saturated fatty acids (SFA). For example, palmitoleic acid and oleic acid protect insulin secreting beta cells against harmful effects palmitic acid induces under high glucose conditions [15–17]. Similarly, MUFA reduce liver steatosis and dysfunction following prolonged periods of high fat diet [18]. Another feature of lipohormesis is the role 4-hydroxyalkenals play in protecting cells against extracellular high levels of glucose and fatty acids [2].

Non-enzymatic peroxidation of polyunsaturated fatty acids (PUFA) is initiated by hydroxyl radical-mediated abstraction of bis-allylic hydrogen atom followed by complex rearrangement and cleavage reactions that ultimately generate three major α,β-unsaturated aldehydes species, depending on specific metabolic pathways of PUFA in cells. The main products are 4-hydroxyl-*2E*-hexenal (4-HHE), 4-hydroxy-2*E*-nonenal (4-HNE) and 4-hydroxy-2E,6Z-dodecadienal (4-HDDE) [19]. All are electrophiles that avidly form covalent adducts with electronegative moieties in macromolecules (i.e., cysteine, lysine, histidine in proteins, ethanolamine in phosphatidylethanolamine, and guanine in DNA) [20–22]. These chemical modifications have been associated with lipid peroxidation-induced damage to cells and in the etiology of various pathologies, such as cancer, atherosclerosis, beta cell dysfunction; hepatic abnormalities, otosclerosis, neurodegenerative diseases, renal diseases, lymphedema, fetal vascular dysfunction in pre-eclampsic pregnancies or in physiological processes like ageing [19,23–26]. In contrast to these and numerous similar studies on the involvement of 4-hydroxyalkenals in disease processes, studies on their hormetic function have gained less attention. This is rather interesting in view of the conclusion Hermann Esterbauer and colleagues drew early in the era of 4-HNE research [27]: "*HNE concentrations below 0.1 μM are likely to occur as basal physiological level in many tissues as well as in serum, and effects observed in this concentration range may therefore be of physiological significance*". Most of the studies on cellular signaling interactions 4-HNE mediates focus on its ability to interact with and modify key proteins in cellular transduction pathways, such as, protein kinase-β (PKCβ), Keap1, platelet-derived growth factor receptors (PDGFR) or mitochondrial uncoupling proteins [2]. Nonetheless, reports on genuine signaling properties of 4-hydroxyalkenals as physiological activators of ligand-activated transcription factors (e.g., peroxisome proliferator-activated receptors (PPARs) have only recently been introduced [28–32]. Fig. 1 shows the main topics of this

Please cite this article as: S. Sasson, Nutrient overload, lipid peroxidation and pancreatic beta cell function, Free Radic. Biol. Med. (2016), http://dx.doi.org/10.1016/j.freeradbiomed.2016.09.003