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Hormetic and regulatory effects of lipid peroxidation mediators in pancreatic beta cells

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ABSTRACT

Nutrient sensing mechanisms of carbohydrates, amino acids and lipids operate distinct pathways that are essential for the adaptation to varying metabolic conditions. The role of nutrient-induced biosynthesis of hormones is paramount for attaining metabolic homeostasis in the organism. Nutrient overload attenuate key metabolic cellular functions and interfere with hormonal-regulated inter- and intra-organ communication, which may ultimately lead to metabolic derangements. Hyperglycemia and high levels of saturated free fatty acids induce excessive production of oxygen free radicals in tissues and cells. This phenomenon, which is accentuated in both type-1 and type-2 diabetic patients, has been associated with the development of impaired glucose tolerance and the etiology of peripheral complications. However, low levels of the same free radicals also induce hormetic responses that protect cells against deleterious effects of the same radicals. Of interest is the role of hydroxyl radicals in initiating peroxidation of polyunsaturated fatty acids (PUFA) and generation of α,β-unsaturated reactive 4-hydroxyalkenals that avidly form covalent adducts with nucleophilic moieties in proteins, phospholipids and nucleic acids. Numerous studies have linked the lipid peroxidation product 4-hydroxy-2*E*-nonenal (4-HNE) to different pathological and cytotoxic processes. Similarly, two other members of the family,

*Chemical compounds studied in this article:*12-HETE (PubChem CID: 5283155); 15-HETE (PubChem CID: 280724); 4-HNA (PubChem CID: 0442150); 12-HpETE (PubChem CID: 5283175); 15-HpETE (PubChem CID: 6437084); 13-HpODE (PubChem CID: 5280720); 13-HODE (PubChem CID: 5282947); 4-Hydroxy-2E,6Z-dodecadienal (PubChem CID: 71340423); 4-Hydroxyl-2E-hexenal (PubChem CID: 5283314); 4-Hydroxy-2E-nonenal (PubChem CID: 5283344); PGD_2 (PubChem CID: 448457); PGE_2 (PubChem CID: 5280360); $PGF_{2\alpha}$ (PubChem CID: 5280363); PGH_2 (PubChem CID: 445049); PGI_2 (PubChem CID: 6436393).
Abbreviations: 4-HDDE, 4-hydroxy-2*E*,6*Z*-dodecadienal; 4-HHE, 4-hydroxyl-2*E*-hexenal; 4-HNA, 4-hydroxynon-2-enoic acid; 4-HNE, 4-hydroxy-2*E*-nonenal; AGE, advanced glycation end products; ADH, alcohol dehydrogenase; AR, aldose reductase; ARE, antioxidant response element; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; COX, cyclooxygenase; DAG, diacylglycerol; EET, epoxyeicosatrienpic acid; EGF, epidermal growth factor; EGRFR, epidermal growth factor receptors; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinases; FALDH, fatty aldehyde dehydrogenase; FDGFR, platelet-derived growth factor receptor; FFA1, free fatty acid receptor 1; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; GLP-1, glucagon-like peptide-1; GP, generalized polarization index; GPx, glutathione peroxidase; GSH, glutathione; GSIS, glucose-stimulated insulin secretion; GST, glutathione-S-transferase; HETE, hydroxyeicosatetraenoic acid; HpETE, hydroperoxyeicosatetraenoic acid; HIF, hypoxia-inducible factor; HpODE, hydroperoxyoctadecadienoic acid; IKK, IκB kinase; IRS, insulin receptor substrate; JUNK, c-Jun N-terminal kinase; Keap1, Kelch-like ECH-associated protein; Lck, lymphocyte-specific protein tyrosine kinase; LT, leukotriene; LO, lipoxygenase; MAPK, mitogen-activated protein kinase; MAPKK, mitogen-activated protein kinase kinase; mTOR, mammalian target of rapamycin; MUFA, monounsaturated fatty acids; Nrf2, nuclear factor (erythroid-derived 2)-like 2; NOS, NO synthase; NOX, NADPH oxidase; NQO1, NAD(P)H:quinone oxidoreductase; PARP, poly(ADP-ribose)-polymerase; PKB/Akt, protein kinase B; PKC, protein kinase C; PDGFR, platelet-derived growth factor receptors; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; PI3K, phosphatidylinositol-3-kinase; PLA2, phospholipase A2; PPARδ, peroxisome proliferator-activated receptor δ; PTEN, phosphatase and tensin homolog; PTP, protein tyrosine phosphatases; PUFA, polyunsaturated fatty acids; ROS, reactive oxygen species; SOD, superoxide dismutase; S6K1, p70 ribosomal protein S6 kinase; sEH, soluble epoxide hydrolase; SFA, saturated fatty acids; SNARE, soluble N-ethylmaleimide-sensitive factor attachment protein receptor; T2DM, type 2 diabetes mellitus; UCP, uncoupling protein; Xpo1, export protein exportin1.

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4-hydroxyl-*2E*-hexenal (4-HHE) and 4-hydroxy-2E,6Z-dodecadienal (4-HDDE), have also been identified as potential cytotoxic agents. It has been suggested that 4-HNE-induced modifications in macromolecules in cells may alter their cellular functions and modify signaling properties. Yet, it has also been acknowledged that these bioactive aldehydes also function as signaling molecules that directly modify cell functions in a hormetic fashion to enable cells adapt to various stressful stimuli. Recent studies have shown that 4-HNE and 4-HDDE, which activate peroxisome proliferator-activated receptor δ (PPARδ) in vascular endothelial cells and insulin secreting beta cells, promote such adaptive responses to ameliorate detrimental effects of high glucose and diabetes-like conditions. In addition, due to the electrophilic nature of these reactive aldehydes they form covalent adducts with electronegative moieties in proteins, phosphatidylethanolamine and nucleotides. Normally these non-enzymatic modifications are maintained below the cytotoxic range due to efficient cellular neutralization processes of 4-hydroxyalkenals. The major neutralizing enzymes include fatty aldehyde dehydrogenase (FALDH), aldose reductase (AR) and alcohol dehydrogenase (ADH), which transform the aldehyde to the corresponding carboxylic acid or alcohols, respectively, or by biding to the thiol group in glutathione (GSH) by the action of glutathione-S-transferase (GST). This review describes the hormetic and cytotoxic roles of oxygen free radicals and 4-hydroxyalkenals in beta cells exposed to nutritional challenges and the cellular mechanisms they employ to maintain their level at functional range below the cytotoxic threshold.

Contents

1. Introduction

Fatty acid metabolism in mammalian cells is complex and serves four main aims: first, for the biosynthesis of phospholipids and membrane biogenesis by the formation of the lipid bilayer permeability barrier of cell and intracellular organelle membranes; second, to serve as an ample source for ATP production via beta oxidation and Krebs cycle; third, to provide numerous lipid mediators that regulate myriad cell functions by acting as signaling molecules that activate receptors in a selective and specific manner; fourth for storage in adipose tissues in the form of triglycerides (Fig. 1). Mammalian cells synthesize saturated fatty acids by the action of acetyl-CoA carboxylase and fatty acid synthase and further generate different monounsaturated fatty acids (MUFA) by the action of target-specific desaturases and elongases. In contrast, linoleic acid and alpha-linolenic acid that are supplied from the diet (hence termed 'essential fatty acids') serve as precursors for the biosynthesis of n-3 and n-6 polyunsaturated fatty acids (PUFA) by a series of targeted desaturation and elongation reactions. Collectively, these varied pathways not only determine the cell's specific lipid composition but also contribute to lipid homeostasis in the organism.

Metabolic stressful conditions such as hyperglycemia and hyperlipidemia, which are common in diabetes, can modulate and modify fatty acid metabolism, membrane lipid composition and alter the generation of lipid mediators and