Abstract

n-3 polyunsaturated fatty acids (PUFAs) are a subgroup of fatty acids with broad health benefits, such as lowering blood triglycerides and decreasing the risk of some types of cancer. A beneficial effect of n-3 PUFAs in diabetes is indicated by results from some studies. Defective insulin secretion is a fundamental pathophysiological change in both types 1 and 2 diabetes. Emerging studies have provided evidence of a connection between n-3 PUFAs and improved insulin secretion from pancreatic \(\beta\)-cells. This review summarizes the recent findings in this regard and discusses the potential mechanisms by which n-3 PUFAs influence insulin secretion from pancreatic \(\beta\)-cells.

Key Words

- n-3 PUFA
- insulin secretion
- islets
- \(\beta\)-cells

Introduction

It is well-known that n-3 polyunsaturated fatty acids (PUFAs), especially eicosapentanoic acid (EPA, 20:5, n-3) and docosahexanoic acid (DHA, 22:6, n-3), have positive effects in a wide range of health and disease conditions. For example, n-3 PUFAs, especially DHA, play a critical role in the development of the CNS (Innis 2007). A diet rich in n-3 PUFAs associated with high seafood intake is thought to be responsible for the low incidence of heart disease in Inuit and Eskimo populations (Dyerberg et al. 1978, Holub 1988, Dewailly et al. 2001). Increased consumption of EPA and DHA is also believed to lower the risk of cancer, hyperlipidemia, hypertension, and neurodegenerative diseases (Siriwardhana et al. 2012).

In the context of diabetes mellitus, n-3 PUFAs have anti-inflammatory and insulin-sensitizing functions (Kalupahana et al. 2011). However, the effect of n-3 PUFAs on insulin secretion from pancreatic \(\beta\)-cells is not well recognized. Defects in insulin secretion are a fundamental pathological event in the development of diabetes, both types 1 and 2. Currently, emerging evidence indicates that n-3 PUFAs may improve insulin secretion from pancreatic \(\beta\)-cells under the conditions of obesity and/or diabetes, but the mechanism is largely unknown. This review provides an update on studies that examine the effects of n-3 PUFAs on insulin secretion or \(\beta\) cell function, and summarizes the potential mechanisms.

n-3 PUFAs: intake and metabolism

PUFAs contain at least two carbon–carbon double bonds. The biologically formed double bond has a cis configuration, which means that hydrogen atoms are oriented on the same side of the double bond. Natural PUFAs are liquid at room temperature, which results from the kink-causing double bonds (cis) in their molecular structure (Das 2006a). PUFAs are named according to the position of the first double bond from the n (ω) end (Fig. 1). The first double bond of n-3 PUFAs is between the number 3 and 4 carbons from the n end (Simopoulos 2000). The main bioactive forms of n-3 PUFA, EPA, and DHA, can be generated from \(\alpha\)-linolenic acid (ALA, C18:3, n-3) in the body by enzyme-catalyzed elongation, desaturation, and \(\beta\)-oxidation (Su 2008). n-3 PUFAs cannot be synthesized de novo in mammals (Das 2006b). Food sources of
Free fatty acids can be taken up by cells and transported inside cells by fatty acid-binding proteins (FABPs) and transported into cells (Iqbal & Hussain 2009). Intra-cellular fatty acids are then transformed into acyl-CoA and directed to the endoplasmic reticulum for esterification to produce other types of lipids such as cholesterol, phospholipids, and triglycerides (Dahlqvist et al. 2000). Twenty-carbon n-3 and n-6 PUFAs can be converted to eicosanoids by cyclooxygenase (COX) and lipoxigenase (LOX) enzymatic pathways (Calder 2010).

### n-3 PUFAs and insulin secretion

Currently, most evidence that supports a promoting effect of n-3 PUFAs on insulin secretion has been obtained from in vitro or ex vivo studies. The Fat-1 transgenic mouse is a unique model for research into n-3 PUFAs, which is genetically modified to express the Caenorhabditis elegans Fat-1 gene. Fat-1 encodes an n-3 fatty acid desaturase, which converts n-6 PUFA to n-3 PUFA (Kang et al. 2004). The fatty acid profile of Fat-1 mice demonstrates significantly higher concentrations of n-3 PUFA and lower concentrations of n-6 PUFA than that of WT mice in many tissues including pancreatic islets without changing the total lipid content of the body (Kang et al. 2004, Wei et al. 2010). In islets isolated from Fat-1 mice, insulin secretion induced by glucose, glucagon-like peptide 1, leucine, and glutamine was found to be enhanced compared with WT islets (Wei et al. 2010). Similarly, in rat insulin-secreting cells (INS1), Fat-1 gene knockin caused the mRNA expression of insulin 1 to increase (Wei et al. 2010). ALA and DHA supplementation of the culture medium enhanced glucose (22 mM)-stimulated insulin secretion (GSIS) in MIN6 mouse insulinoma cells (Itoh et al. 2003). In both INS1 cells and cultured mouse islets, EPA supplementation restored saturated fatty acid (palmitate)-mediated inhibition of insulin secretion (Kato et al. 2008, Shao et al. 2010). The palmitate-induced mRNA and nuclear expression of a key transcription factor regulating lipogenesis, sterol regulatory element-binding protein 1c (SREBP1c), is inhibited by EPA (Kato et al. 2008). However, EPA did not influence glucose/KCl-induced insulin secretion in the absence of palmitate, indicating that EPA may protect pancreatic β-cells by preventing palmitate-mediated upregulation of SREBP1c (Kato et al. 2008).

In vivo animal model data on the effect of n-3 PUFAs on insulin secretion are limited and some inconsistencies exist. Fat-1 mice treated with the β-cell toxin streptozotocin are protected from developing hyperglycemia, β-cell destruction, and hypoinsulinemia (Bellenger et al. 2011). Conversely, provision of an EPA/DHA-enriched diet for 7 months did not influence plasma glucose, insulin, or C-peptide during an oral glucose tolerance test in pigs (Castellano et al. 2010). Whether these differences are a
consequence of the animal model or of a lack of diabetes insulin in the pigs is unclear. Human data are likewise conflicting. In overweight hyperlipidemic men, both EPA and DHA treatment for 6 weeks increased fasting insulin significantly (Mori et al. 2000), but in type 2 diabetic patients 6-week EPA/DHA treatment had no effect on fasting insulin or C-peptide (Woodman et al. 2002). The inconsistencies might due to the species studied, a lack of control over the amount of fatty acid absorbed, or the length of fatty acid treatment.

**Proposed mechanisms for the effect of n-3 PUFAs on insulin secretion**

**Lipid raft structure/function modulation**

Specific cell membrane microdomains termed lipid rafts are involved in the insulin secretion process (Xia et al. 2004). As a membrane component, n-3 PUFAs may regulate membrane structure and properties and therefore influence the insulin secretion process. Dietary or in vitro EPA/DHA supplementation decreases arachidonic acid (AA, C20:4, n-6) and increases EPA/DHA abundance in membranes, whole cells, and tissues, resulting in alterations in membrane structure and fluidity, protein distribution in the membrane, and signal transduction (Jump 2002, Anderson & Ma 2009).

The classic fluid mosaic model of membranes has been challenged for years and some aspects of the concept have been proven untrue (Catala 2012, Bagatolli & Mouritsen 2013). The distribution of membrane molecules seems to not be random, but is organized in some way. Lipid rafts have distinct components and structure and play a vital role in membrane-associated signaling and trafficking (Simons & Toomre 2000, Hanzal-Bayer & Hancock 2007).

Lipid rafts contain concentrated cholesterol, sphingolipid, transmembrane proteins, glycosphatidylinositol-anchored proteins, and acylated proteins relative to nonraft regions (Calder & Yaqoob 2007). Furthermore, higher levels of long-chain saturated fatty acids are found in phospholipids in lipid rafts compared with non-raft regions (Brown & London 2000). As a result, lipid rafts are believed to be in a liquid-ordered state, characterized by lower fluidity, higher melting temperature, and insolubility in nonionic detergents (London & Brown 2000). Lipid rafts facilitate membrane signaling with harbored molecules such as receptors, adaptors, kinases, and lipids required for signal initiation and transduction. Lipid rafts are found not only in plasma membranes but also in intracellular membranes such as the Golgi complex in all cell types, including pancreatic β-cells (Nichols et al. 2001).

Lipid rafts are associated with the cellular glucose transport activity of glucose transporter 2 (GLUT2) in β-cells (Ohtsubo et al. 2013). Increased localization of GLUT2 in lipid rafts leads to less glucose transport, due to high GLUT2-binding stomatin content in the rafts of pancreatic β-cells (Ohtsubo et al. 2013). The disruption of lipid rafts by methyl-β-cyclodextrin, a specific cholesterol binding agent, enhances glucose transport by releasing GLUT2 to nonraft membrane regions (Ohtsubo et al. 2013). Methyl-β-cyclodextrin also promotes closure of Kᵥ2.1 potassium but not Caᵥ1.2 calcium channels, and enhances insulin granule exocytosis (Xia et al. 2004). It is well documented that incorporation of n-3 PUFAs disrupts lipid raft function in several cell types (Fan et al. 2003, Garattini 2007). For example, in human T-cells, incorporation of DHA into lipid rafts results in a shift of expression of interleukin 2 receptor α (IL2Rα), with more relocated to non-raft regions and this is associated with altered signal transduction via specific pathways (Li et al. 2005). In human breast cancer cells, EPA and DHA treatments decrease cholesterol, sphingomyelin, and diacylglycerol content and increase ceramide content in lipid rafts (Schley et al. 2007). Thus, it is likely that n-3 PUFAs disrupt properties and functions of lipid rafts in pancreatic β-cells as in other cell types, and may have similar effects on GLUT2 localization and ion channel activity to methyl-β-cyclodextrin, which would result in enhancement of insulin secretion.

**Inhibition of pro-inflammatory mediators**

Obesity, a major risk factor for type 2 diabetes, is accompanied by insulin resistance and chronic low-grade inflammation (Shoelson et al. 2007). Adipose tissue inflammation is believed to play a crucial role in the development of impaired insulin secretion in type 2 diabetes (Arruda et al. 2011).

An important group of pro-inflammatory mediators produced by adipocytes and pancreatic β-cells is the eicosanoids, signaling molecules that modulate a broad range of body functions (Calder 2010, Fan et al. 2013). Eicosanoids, including prostaglandins (PG), leukotrienes (LT), thromboxanes, and lipoxins, can be made by oxidation of 20-carbon n-3 and n-6 PUFAs, including EPA (n-3), AA (n-6) and dihomo-γ-linolenic acid (DGLA, 20:3, n-6) (Tapiero et al. 2002). AA-derived eicosanoids are potent pro-inflammatory mediators. However, three-series PG and five-series LT from EPA are weaker than AA-derived
two-series PG and four-series LT in promotion of vasodilation, smooth muscle contraction, vascular permeability, and leukocyte recruitment (Calder 2006). In addition, resolvins and protectins are newly discovered bioactive n-3 PUFA derivatives (Spite & Serhan 2010). E-series resolvins synthesized from EPA and protectins and D-series resolvins synthesized from DHA have anti-inflammatory properties (Kohli & Levy 2009). Furthermore, the generation of eicosanoids from n-3 PUFA and n-6 PUFAs is catalyzed by the same enzymes, COX and LOX (de Roos et al. 2009). Therefore, increased provision of n-3 PUFA results in reduced synthesis of highly pro-inflammatory eicosanoids from AA. PG (one-series) from DGLA are anti-inflammatory eicosanoids; however, the amount of DGLA in the body is about tenfold lower than that of AA (Umeda-Sawada et al. 2006). Thus, n-3 PUFAs are considered to be more protective against inflammation compared with n-6 PUFAs (Fig. 2).

With respect to pancreatic islet function, PGE\(_2\) is a known inhibitor of GSIS (Seaquist et al. 1989). COX2 gene expression and PGE\(_2\) synthesis are induced by IL1\(\beta\) in isolated rat islets and various cell lines (Tran et al. 1999). AA supplementation induces PGE\(_2\) production in rat insulinoma cells RINm5F (Han et al. 2002) but INS1 cells and islets that are genetically modified to express the Fat-1 transgene produce less PGE\(_2\) under an AA challenge (Wei et al. 2010). As mentioned previously, the Fat-1 gene enables the conversion of n-6 PUFA to n-3 PUFA in cells and results in a much lower n-6/n-3 fatty acid ratio (Kang 2007). Thus, altering the n-6/n-3 profile may help to restore GSIS impaired by pro-inflammatory eicosanoids present in chronic inflammation.

Besides reducing the production of pro-inflammatory eicosanoids from n-6 PUFA, n-3 PUFAs are also effective in inhibition of synthesis pro-inflammatory cytokines. Tumor necrosis factor (TNF) and IL1\(\beta\) are known to trigger apoptosis of islets. However, cell death induced by TNF and IL1\(\beta\) is significantly alleviated in Fat-1 islets compared with WT islets, as a result of suppressed activation of nuclear factor kappa B (Nf\(\kappa\)B) and ERK (Wei et al. 2010). Eight weeks of n-3 PUFA treatment in obese people has been shown to decrease gene expression of pro-inflammatory cytokines in subcutaneous adipose tissue and reduce the level of inflammatory markers in plasma (Itariu et al. 2012). Thus, n-3 PUFA may contribute to the production of insulin secretion by reducing the amount of insulin-suppressing pro-inflammatory cytokines, such as IL1\(\beta\) and TNF in circulation (Hughes et al. 1990, Zhang & Kim 1995).

**Binding to G-protein-coupled receptors**

It is reported that n-3 PUFA modulates insulin secretion from pancreatic \(\beta\)-cells through a free fatty acid receptor, G-protein-coupled receptor 40 (GPR40). Both medium- and long-chain free fatty acids can bind GPR40 (Briscoe...
et al. 2003, Mancini & Poitout 2013). ALA, EPA, and DHA are all ligands for GPR40 with EC_{50} values in the micromolar range (Grill & Qvigstad 2000). Human brain and pancreas have high levels of expression of GPR40 (Yonezawa et al. 2013). In particular, the pancreatic β-cells, as well as β-cell lines including MIN6 (mouse insulinoma cells), HIT-T15, RINm5F, and ßTC-3, all express GPR40 (Grill & Qvigstad 2000). GPR40 is involved in insulin secretion of pancreatic β-cells in response to linoleic acid (Salehi et al. 2005). In immune cells, GPR40 is only detected in monocytes (Mancini & Poitout 2013). The macrophages are the main infiltrating inflammatory cells derived from monocytes in adipose tissue in obese and type 2 diabetes patients (Weisberg et al. 2003, Heilbronn & Campbell 2008) and islet infiltration by macrophages is increased in type 2 diabetic human patients and mice (Ehses et al. 2007). The role of GPR40 in macrophage function as it relates to development of insulin secretion defects in type 2 diabetes is therefore worth investigating.

Binding of fatty acids to GPR40 leads to activation of G_{q_{\alpha}}, phosphorylation of phospholipase Cβ (PLCβ), and subsequent generation of inositol 1,4,5-trisphosphate (IP_{3}) and diacylglycerol (DAG) through hydrolysis of phosphatidylinositol 4,5-bisphosphate. IP_{3} binds to the receptors on endoplasmic reticulum and causes intracellular Ca^{2+} to rise, which is a key event leading to the release of stored insulin from insulin granules. DAG activates protein kinase Cα and protein kinase D, which contribute to the depolymerization of actin and the facilitation of insulin granule mobilization (Rutter 2003). ALA and DHA amplify GSIS in MIN6 cells stimulated with 22 mM glucose by binding to GPR40 and causing Ca^{2+} influx and MAPK activation (Itoh et al. 2003). Thus, GPR40 might be a target through which n-3 PUFAs enhance insulin secretion in β-cells.

GPR120 is another GPR to which long-chain free fatty acids, with preference for PUFA, bind (Oh & Olefsky 2012). In humans, GPR120 expression is detected in adipose tissue, colon, lung, trachea, and macrophages (Oh et al. 2010, Oh & Olefsky 2012). Using human epithelial colorectal adenocarcinoma cells (Caco-2), GPR120 was shown to bind both n-3 (EPA and DHA) and n-6 (AA) PUFAs, and similar signaling pathways were initiated (Mobraten et al. 2013). However, EPA/DHA and AA have different potencies on inducing Ca^{2+} mobilization and activating ERK. AA is a more potent enhancer of Ca^{2+} level and a less potent inducer of ERK activation (Mobraten et al. 2013). GPR120 modulates inflammatory responses as shown by experiments, in which GPR120 knockdown attenuated the ability of DHA to suppress lipopolysaccharide-induced TNF and IL6 production in mouse leukemic monocyte/macrophage cells and primary intraperitoneal macrophages (Oh et al. 2010). Dysfunction of GPR120 is associated with energy imbalance and obesity in both humans and rodents (Ichimura et al. 2012), indicating that GPR120 activation by n-3 PUFA has the potential to alleviate inflammation associated with macrophages and adipocytes, which is important in the pathogenesis of type 2 diabetes and involved in impaired insulin secretion as discussed previously.

Binding to nuclear receptors

n-3 PUFAs and their metabolic derivatives are known ligands for peroxisome proliferator-activated receptors (PPARs; Zuniga et al. 2011), which function together with retinoid-X receptors as nuclear receptors and regulate lipid metabolism, inflammation, immune function, and cell proliferation and differentiation (Peters et al. 2012). NFκB is a key transcription factor regulating the expression of pro-inflammatory cytokines (Lawrence 2009) and its interaction with PPAR limits its translocation to the nucleus (Chen et al. 2009, Ogawa et al. 2012). Thus, PPAR activation inhibits the production of inflammatory mediators such as TNF and IL1β (Chinetti et al. 2003). There are three known members of the PPAR family – PPARα, PPARβ/δ, and PPARγ – which have different tissue distribution and function. PPARβ/δ is present throughout the body, whereas liver and adipose tissue have high expression levels of both PPARx and PPARγ (Braissant et al. 1996). PPARα mainly regulates genes involved in fatty acid oxidation (Kersten et al. 1999), while PPARγ modulate genes involved in lipogenesis, insulin signaling, and inflammation (Mueller et al. 2002). Pancreatic β-cells express all three members of the PPAR family (Zhou et al. 1998).

Although results from studies of the regulatory effect of PPARs on insulin secretion are not consistent, they do indicate that PPARs have the potential to modulate insulin secretion directly. Pre-incubation with PPARγ agonist for 48 h amplified insulin secretion induced by 20 mM glucose in INS1 cells, without changing cell insulin content (Santini et al. 2004). In another study, PPARγ activation was shown to enhance GSIS and increase mRNA expression of GPR40 and GLUT2 by inducing intracellular calcium mobilization in INS1 cells and primary rat islets (Kim et al. 2013). However, PPARγ knockin resulted in decreased GSIS in INS1 cells (Ravnskjaer et al. 2005). In the same study, PPARγ knockin caused GSIS to increase (Ravnskjaer et al. 2005), but other researchers showed...
that PPAR\(\alpha\) activation is associated with increased UCP2 expression and inhibited GSIS in mouse islets and INS1 cells (Triantafilou \etal\, 2002, Fatehi-Hassanabad \& Chan 2007). PPAR\(\beta/\delta\) activation with an agonist amplifies GSIS in response to 20 mM glucose in INS1 cells and isolated rat islets (Cohen \et\, 2011). However, PPAR\(\beta/\delta\)-deficient islets had elevated GSIS compared with WT (Iglesias \et\, 2012). These results indicate that PPARs might be the targets through which n-3 PUFAs alter insulin secretion directly, but their effect seems to be dependent on specific conditions. More investigations are required in order to draw a clear conclusion.

PPAR activation has also been shown to inhibit the expression of pro-inflammatory cytokines in T-cells and macrophages, therefore n-3 PUFA activation of PPARs may contribute to the alleviation of inflammation in diabetes, thereby conferring protection against inflammation-impaired insulin secretion (Clark 2002).

**Induction of adipokines**

Adiponectin is one of the adipokines most abundantly produced by adipose tissue and is a key regulator of fatty acid and glucose metabolism (Karbowska \& Kochan 2006). Adiponectin receptors are expressed in human and mouse pancreatic \(\beta\)-cells (Kharroubi \et\, 2003). Adiponectin protects \(\beta\)-cells from apoptosis induced by pro-inflammatory cytokines and saturated fatty acids (Wijesekara \et\, 2010, Jian \et\, 2013). \textit{In vivo}, i.v. injection of adiponectin significantly increased plasma insulin concentration in C57BL/6 mice (Okamoto \et\, 2008). \textit{In vitro}, adiponectin promotes mRNA expression of insulin (Wijesekara \et\, 2010) and amplifies GSIS by boosting fatty acid \(\beta\)-oxidation in both human pancreatic islets and INS1 cells (Patane \et\, 2013). Adiponectin is also shown to augment insulin secretion from mouse pancreatic islets under the stimulation of 5.6 mM glucose by promoting insulin granule transport and fusion with plasma membrane (Okamoto \et\, 2008). Results from another \textit{in vitro} study indicate that the effect of adiponectin on insulin secretion is correlated with insulin sensitivity, because adiponectin augmented GSIS in islets from insulin-resistant mice, but not in normal islets (Winzell \et\, 2004). In pancreatic \(\beta\)-cells, the activation of adiponectin receptor may lead to the stimulation of AMP-activated protein kinase, elevation of intracellular calcium (Yamauchi \et\, 2003), and enhanced phosphorylation of ERK and AKT (Wijesekara \et\, 2010). Extracellular nicotinamide phosphoribosyltransferase (eNampt, also called visfatin) is another adipokine that regulates \(\beta\)-cell function. Treatment with eNampt for 1 h significantly enhances insulin secretion from \(\beta\)-TC6 cells in the presence of 2.2 mM glucose (Brown \et\, 2010). The promoting effect of eNampt on insulin secretion is believed to be mediated by increased NAD biosynthesis (Revollo \et\, 2007). eNampt also induces the activation of insulin receptor and ERK (Brown \et\, 2010). In obesity, adipocytes produce FABP4, which synergistically enhances insulin secretion with linoleate without influencing the insulin secretion from pancreatic \(\beta\)-cells. n-3 PUFAs may promote insulin secretion from pancreatic \(\beta\)-cells indirectly by inducing the production of the adipokines (adiponectin and eNampt) from adipose tissue, and inhibiting production of pro-inflammatory cytokines and eicosanoids from AA. Action on adiponectin receptors would promote insulin secretion while the inhibitory effects of cytokine-receptor-mediated actions would be dampened. n-3 PUFAs may also directly affect \(\beta\)-cell function via alterations in lipid raft function, or by binding to PPARs, GPR40 and GPR120. AA, arachidonic acid; GPR, G protein-coupled receptor; PPARs, peroxisome proliferator-activated receptors; PUFA, polyunsaturated fatty acids. A full colour version of this figure is available via http://dx.doi.org/10.1530/JOE-14-0581.
supplementation normalizes adiponectin secretion partly through suppressing production of TNF by macrophages (Itoh et al. 2007). EPA has also been shown to promote secretion and mRNA expression of eNAMPT in primary mouse adipocytes in an AMP-activated protein-kinase-dependent manner (Lorente-Cebrian et al. 2009). Thus, n-3 PUFAs may help to maintain insulin secretion from β-cells by stimulating production of adiponectin and eNamt from adipose tissue.

Summary and conclusion

Direct enhancement of insulin secretion by n-3 PUFAs is indicated by the results of some studies, mostly in vitro. The in vivo data and human studies have inconsistent outcomes, indicating that the species of n-3 PUFAs, length of fatty acid treatment, how they are provided, and the specific physiological state are important for the effect of n-3 PUFAs on insulin secretion and β cell function. n-3 PUFAs may be able to modulate insulin secretion from pancreatic β-cells directly by altering lipid raft structure and function, and binding to receptors including PPAR, GPR40, and GPR120, and indirectly by promoting adipokine production and inhibiting the expression of pro-inflammatory mediators in adipose tissue (Fig. 3). However, these hypotheses have not been stringently tested. n-3 PUFAs may have value as supplements to prevent or slow down the impairment of insulin secretion in diabetes, and to decrease the use of anti-diabetic drugs, which warrants more comprehensive studies.

Declaration of interest

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