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Review

Arachidonic acid and lipoxin A_4 as possible endogenous anti-diabetic molecules

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ABSTRACT

In both type 1 and type 2 diabetes mellitus, increased production of pro-inflammatory cytokines and reactive oxygen species (ROS) occurs that induce apoptosis of β cells and cause peripheral insulin resistance respectively though the degree of their increased production is higher in type 1 and less in type 2 diabetes mellitus. Despite this, the exact mechanism(s) that lead to increased production of pro-inflammatory cytokines: interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) and ROS is not known. Studies showed that plasma concentrations of arachidonic acid (AA) and lipoxin A_4 (LXA_4) are low in alloxan-induced type 1 diabetes mellitus in experimental animals and patients with type 2 diabetes mellitus. Prior administration of AA, eicosapentaenoic and docosahexaenoic acids (EPA and DHA, respectively) and transgenic animals that produce increased amounts of EPA and DHA acids were protected from chemical-induced diabetes mellitus that was associated with enhanced formation of LXA_4 and resolvins, while protectin D_1 ameliorated peripheral insulin resistance. AA, LXA_4, resolvins and protectins inhibit IL-6 and TNF-α production and suppress ROS generation. Thus, AA and lipoxins, resolvins and protectins may function as endogenous anti-diabetic molecules implying that their administration could be useful in the prevention and management of both types of diabetes mellitus.

1. Introduction

Diabetes mellitus (DM), characterized by hyperglycemia, is due to defects in insulin secretion and/or action. Chronic persistent hyperglycemia of DM leads to dysfunction, damage or failure of target tissues and organs such as the eyes, kidneys, heart, vascular tissue, and nerves. The DM is classified into two types: *type 1 diabetes* and *type 2 diabetes*. In type 1 DM, development of DM is due to autoimmune destruction of pancreatic β cells with consequent insulin deficiency and hence these patients are dependent on insulin from external sources. Patients with type 2 diabetes mellitus are not insulin deficient but show increased peripheral insulin resistance and consequent hyperinsulinemia, who over a period of time also become insulin deficient due to the exhaustion of pancreatic β cells and hence, may eventually become insulin dependent.

Studies suggested that pro-inflammatory cytokines: interleukin-1 (IL-1), IL-2, IL-6, tumor necrosis factor-α (TNF-α) and macrophage migration inhibitory factor (MIF), inducible nitric oxide (iNO), superoxide anion and other free radicals participate in the pathobiology of diabetes mellitus. Damage to pancreatic β cells as a result of release of TNF-α and IL-1 produced by infiltrating macrophages, lymphocytes and monocytes leads to the development of type 1 DM [1,2]. In the model of multiple low-dose streptozotocin-induced diabetes in rats and mice, it was observed that high levels of IL-2, interferon-γ (IFN-γ), and TNF-α produced by T_H1 lymphocytes activate macrophages and promote destruction of β cells both by nitric oxide (NO) and non-NO-mediated mechanisms [3]. Human duct cells, which are in a close topographic relationship with β cells, are a source of TNF-α that has been implicated in the development of autoimmune diabetes in mice [4]. Macrophage migration inhibitory factor (MIF) produced by macrophages also plays a significant role in the development of type 1 diabetes mellitus. MIF-mRNA expression in splenic lymphocytes was up regulated during the development of cell-mediated diabetes (type 1 diabetes mellitus) in non-NOD (non-obese diabetic) mice [5]. Further, treatment of NOD mice with recombinant MIF-protein from age 6 to 11 weeks, led to an increased diabetes incidence compared with untreated control groups at week 34 suggesting a role of MIF in autoimmune-inflammatory type-1 diabetes [5]. TNF-α [6,7] could stimulate MIF production; TNF-α and MIF may act in concert with each other to produce damage to pancreatic β cells and induce type 1 diabetes.

Type 2 diabetes mellitus is more prevalent than type 1 diabetes and it accounts for more than 90% of those with diabetes.

It is known that low-grade systemic inflammation plays a significant role in the pathogenesis of type 2 diabetes [8,9] since,

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plasma concentrations of C-reactive protein (CRP), TNF-α, IL-6, and resistin, which are markers of inflammation, are elevated whereas the concentrations of adiponectin that is anti-inflammatory in nature are reduced in type 2 DM [10–12]. Both IL-6 and TNF-α increase neutrophil superoxide anion generation [13,14]. Superoxide anion (O_2^-) inactivates eNO and prostacyclin (PGI_2) and thus causes endothelial dysfunction and peripheral insulin resistance. Thus, an increase in oxidative stress could an important factor contributing to the development of type 2 diabetes.

Based on these evidences, it is suggested that suppression of excess production of IL-6, TNF-α, MIF and reactive oxygen species could be of benefit in the prevention and management of both type 1 and type 2 diabetes mellitus.

2. Metabolism of essential fatty acids with specific reference to inflammation

Cis-linoleic acid (LA, 18:2 $\omega-6$) and α-linolenic acid (ALA, 18:3 $\omega-3$) are called as "essential fatty acids" (EFAs) since they cannot be formed in the body. LA is converted to gamma-linolenic acid (GLA, 18:3, $\omega-6$) by the enzyme Δ^6 desaturase, and GLA, in turn, is elongated to form di-homo-GLA (DGLA, 20:3, $\omega-6$), the precursor of the 1 series of prostaglandins. DGLA can be converted to arachidonic acid (AA, 20:4, $\omega-6$) by the enzyme Δ^5 desaturase, the precursor of 2 series of prostaglandins, thromboxanes and the 4 series leukotrienes (LTs). AA is also converted into non-enzymatic lipid mediators: 4-hydroxynonenal, isoprostanes, isoketals and isofurans in tissues by non-enzymatic reactions catalyzed by free radicals in vivo and are believed to be useful as markers for oxidative stress.

Similar to $\omega-6$ LA, ω-3 ALA is converted to eicosapentaenoic acid (EPA, 20:5, $\omega-3$) by Δ^6 and Δ^5 desaturases, the precursor of the three series of prostaglandins and the 5 series of LTs. EPA can be elongated to form docosahexaenoic acid (DHA, 22:6, $\omega-3$). AA, EPA and DHA also give rise to anti-inflammatory lipoxins; resolvins, protectins and maresins [15–26] (see Figs. 1–3 for metabolism of EFAs and the formation of lipoxins and resolvins). Eicosanoids bind to G protein-coupled receptors and mediate many steps of inflammation [27–29]. Non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin inhibit cyclo-oxygenase (COX) activity and thus, bring about their anti-inflammatory action.

The general purpose of lipoxins and similar compounds generated from AA, EPA and DHA is not only to suppress the production of pro-inflammatory prostaglandins, thromboxanes, leukotrienes and isoprostanes but also to limit inflammation, enhance wound healing and resolve inflammation and thus, restore cell, tissue and organ function to normal. Hence, when the formation of lipoxins is defective or subnormal, it could lead to persistent inflammation and tissue injury [24]. Hence, it is proposed that decreased formation of lipoxins when pancreatic β cells are exposed to toxic agents such as IL-6, TNF-α and MIF could lead to β cell dysfunction or destruction and the onset of diabetes.

3. Anti-inflammatory cytokines IL-4 and IL-10 enhance LXA_4 synthesis

In this context, it is noteworthy that anti-inflammatory cytokines IL-4 and IL-10 trigger the conversion of AA, EPA and DHA to lipoxins, resolvins and protectins suggesting a mechanism by which they are able to suppress inflammation [30]. IL-4 up-regulated 15-LO gene expression in human leukocytes suggesting that IL-4 promoted anti-inflammatory actions by enhancing LXA_4 formation.

3.1. PUFAs and lipoxins bind to GPCR to suppress inflammation

Monocytes and macrophages express many G protein-coupled receptors (GPCRs) that regulate inflammation and immunity [27–29]. PUFAs, especially AA, EPA and DHA and their metabolites such as eicosanoids, lipoxins, resolvins, protectins and maresins function as agonists at a number of G protein-coupled receptors (GPCRs). Tissue distribution studies and siRNA knock-down experiments have indicated key roles for these GPCRs in glucose homeostasis, adipogenesis, leukocyte recruitment and inflammation [27–33]. In a recent study [29], it was shown that the G protein-coupled receptor 120 (GPR120) functions as a $\omega-3$ fatty acid receptor/sensor. Stimulation of GPR120 with $\omega-3$ fatty acids (EPA and DHA) induced broad anti-inflammatory effects in monocytic RAW 264.7 cells and in primary intraperitoneal macrophages, effects that were abrogated by GPR120 knockdown. The $\omega-3$ fatty acid treatment not only inhibited inflammation but also enhanced systemic insulin sensitivity in wild-type mice, but was without effect in GPR120 knockout mice, suggesting that GPR120 is a functional $\omega-3$ fatty acid receptor/sensor and mediates potent insulin sensitizing and antidiabetic effects in vivo by repressing macrophage-induced tissue inflammation [29]. Thus, PUFAs and their anti-inflammatory products: lipoxins, resolvins, protectins and maresins inhibit the production of various pro-inflammatory molecules including MIF and HMGB1 and thus, suppress inflammation in diseases such as diabetes mellitus.

3.2. Hypothesis: A deficiency of LXA_4 may be responsible for diabetes mellitus

Based on the preceding discussion, it is suggested that a deficiency of LXA_4 that has anti-inflammatory actions may perpetuate inflammation in diabetes mellitus. Hence, I propose that decreased production of LXA_4 and resolvins may lead to infiltration of leukocytes and macrophages to pancreas that ultimately produce damage to β cells and the onset of type 1 diabetes mellitus and its (LXA_4 and resolvins) and/or its precursors (AA, EPA and DHA) deficiency leads to peripheral insulin resistance since these compounds have potent inhibitory action on the synthesis of IL-6, TNF-α and HMGB1 and suppress free radical generation [34–39]. Evidences in favour of this proposal are detailed below.

3.3. PUFAs, lipoxins, resolvins and protectins in diabetes mellitus

Previously, my colleagues and I showed that alloxan-induced cytotoxicity to pancreatic β cells in vitro and alloxan-induced DM (that is similar to type 1 DM) can be prevented by pre-treatment and/or simultaneous treatment of experimental animals with AA, EPA and DHA [40–42] as shown in Figs. 4 and 5 and Table 1. Subsequent studies showed that both cyclo-oxygenase (COX) and lipoxygenase (LOX) inhibitors do not block the beneficial action of PUFAs, suggesting that fatty acids themselves are effective in preventing the diabetogenic action of alloxan. In an extension of this study, it was noted that plasma levels of GLA, DGLA, and AA of $\omega-6$ series and DHA of $\omega-3$ series are particularly decreased in alloxan-induced diabetic animals (Table 1). Of all, the decrease in AA seems to be significant since, it is this fatty acid that is most effective in protecting experimental animals from developing alloxan-induced diabetes (see Table 2). This implies that AA has a significant role to play in the pathobiology of diabetes mellitus.

It was also observed that plasma AA content of the PL fraction is low in WNIN/Ob and WNIN/GR-Ob rats, which develop obesity and glucose intolerance spontaneously and are genetically prone to develop obesity and other features of metabolic syndrome [43] (see Table 3). This is further supported by the observation that