Potential role of polyunsaturated fatty acids in diabetic retinopathy

Junhui Shen¹, Yan-Long Bi¹, Undurti N. Das²

¹Department of Ophthalmology, Tongji Hospital Affiliated to Tongji University School of Medicine, Shanghai, China
²UND Life Sciences, USA

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Abstract

Diabetic retinopathy (DR) is a serious complication of long-standing diabetes mellitus. It affects about 25% of all patients with diabetes mellitus and causes a significant decrease in the quality of life. Despite many years of research, the exact pathway that leads to the development and progression of DR is not clear. Recent studies suggest that polyunsaturated fatty acids (PUFAs) and their metabolites could play a significant role in DR. There is evidence to suggest that an imbalance between pro- and anti-inflammatory eicosanoids and enhanced production of pro-angiogenic factors may initiate the onset and progression of DR. This implies that PUFAs and their metabolites that possess anti-inflammatory actions and suppress the production of angiogenic factors could be employed in the prevention and management of DR.

Key words: vascular endothelial growth factor, hemorheology, inflammation, brain-derived neurotrophic factor, diabetic retinopathy, polyunsaturated fatty acids.

Introduction

Diabetes retinopathy (DR), a major cause of visual impairment in adults [1, 2], is estimated to affect approximately 19–50% depending on the type of retinopathy and ethnicity of the patients [3, 4]. Though the exact mechanism(s) that initiates and renders DR progression are not clear, there is evidence to suggest that oxidative stress [5, 6], retinal vascular endothelial dysfunction [7] and consequent increased vascular permeability [8], enhanced expression of adhesion molecules [9, 10] and increased production and action of pro-inflammatory cytokines play a significant role [11, 12] suggesting that DR is a low-grade inflammatory condition. Since the retina is rich in n-3 polyunsaturated fatty acids (PUFAs), and their metabolites lipoxins, resolvins and protectins have anti-inflammatory actions, these molecules may have a role in DR.

Metabolism of essential fatty acids

Essential fatty acids (EFAs) n-3 α-linolenic acid (ALA) and n-6 linoleic acid (LA) are widely distributed in our diet. It is believed that both n-3 and n-6 EFAs are metabolized by the same set of enzymes Δ⁶ and Δ⁵ desaturases and elongases into their long-chain metabolites, ALA to eicosapentaenoic and docosahexaenoic acids (eicosapentaenoic acid (EPA)
and docosahexaenoic acid (DHA) respectively) and LA to arachidonic acid (AA) (Figure 1) [13–15]. Both EFAs and their long-chain metabolites AA, EPA and DHA are incorporated mainly into the phospholipid (PL) fraction of the cell membrane. In response to various stimuli including growth factors, cytokines and free radicals, phospholipase A₂ (PLA₂) is activated leading to the release of AA, EPA and DHA, which are converted to their respective eicosanoids. The AA, EPA and DHA are metabolized by cyclo-oxygenases (COXs), lipoxygenases (LOXs), and cytochrome P450 (CYP450) enzymes, which results in the formation of several products (Figure 2). The AA forms a precursor to pro-inflammatory prostaglandins and thromboxanes of 2 series and leukotrienes of 4 series (though not all prostaglandins formed are pro-inflammatory. For instance prostacyclin from AA and prostaglandin E₁

![Figure 1. Scheme showing metabolism of essential fatty acids, their role in inflammation and factors that influence DR)](image-url)
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(PGE₁) from DGLA have anti-inflammatory actions), whereas EPA forms precursor to 3 series prostaglandins, thromboxanes and prostacyclins. It is noteworthy that AA can also give rise to lipoxins, which are potent anti-inflammatory molecules. Similarly, EPA gives rise to resolvins and DHA to protectins, which possess significant anti-inflammatory and wound healing properties and show cytoprotective actions. Thus, AA, EPA and DHA, under defined conditions, form specific anti-inflammatory lipoxins, resolvins and protectins respectively that protect various cells and tissues against insults and augment recovery of the target tissues and organs to normal and reestablish homeostasis. Since the retina and brain are rich in AA, DHA and EPA (DHA > AA > EPA), it is reasonable to assume that adequate amounts of lipoxins, resolvins and protectins are formed under normal physiological conditions to protect the retina and other neuronal cells from various insults and diseases [13–15]. This evidence indicates that PUFAs are not only biologically active by themselves but are also capable of giving rise to several biologically active metabolites that play an important role in physiological and pathological processes.

**Inflammation plays a role in diabetic retinopathy**

There is reasonable evidence to suggest that DR is an inflammatory condition. But, unlike the classical inflammatory signs such as pain (dolor), heat (calor), redness (rubor), swelling (tumor), and loss of function (functio laesa) [16], the inflammatory signs in DR are more at the microscopic level. The features of inflammation seen in DR include vessel dilatation, altered flow, exudation of fluids including plasma proteins, and leucocyte accumulation and migration [17]. These local microscopic signs of inflammation in DR are due to increased production of tumor necrosis factor-α (TNF-α), vascular endothelial growth factor (VEGF), prostaglandins (PGs), enhanced expression of intercellular adhesion molecule-1 (ICAM-1) on the vasculature, β2 integrins on the leucocytes, and vascular cell adhesion molecule-1 (VCAM-1) and VLA-4 (very late antigen-4, also called integrin α4β1) [11, 12, 18–20]. These events enhance leucocyte adherence and accumulation within the vasculature of the retina [21], which may precede the occurrence of DR. The leucocyte adherence and migration lead to vascular dysfunction as a result of increased production of reactive oxygen species (ROS) and lipid peroxidation that occurs locally, which results in a subtle breakdown of the blood-retinal barrier, premature endothelial cell injury and death, and capillary ischaemia/reperfusion [22]. This evidence is supported by the observation that in diabetic rats treated with ICAM-1 or β2 integrin neutralizing antibodies, leucocyte adhesion is suppressed [18, 19], blood-retinal barrier breakdown is normalized [18] and endothelial cell injury and death are prevented [22]; mice deficient in the ICAM-1 or β2 integrin gene CD18 when made diabetic have near normal retinal vasculature [23]; patients with rheumatoid arthritis receiving high doses of aspirin tended to have less severe diabetic retinopathy [24]; and aspirin prevented histopathological features of DR [16].

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**Figure 2.** Metabolism of AA after its release from cell membrane lipid pool by the activation of phospholipase A2 on exposure to hormones, growth factors and cytokines. The PGHSs metabolize AA to prostaglandins, thromboxanes and prostacyclins. LOXs metabolize AA to leukotrienes, hydroxyeicosatetraenoic acids (HETEs) and lipoxins. The P450 monoxygenases metabolize AA to mid-chain HETEs, ω-3 terminal HETEs and the epoxyeicosatrienoic acids (EETs). The EETs have anti-inflammatory actions and so are likely to play a role in DR. Even EPA undergoes the same metabolic fate as is shown for AA here.
A direct correlation between retinal VEGF expression and diabetic blood-retinal barrier breakdown [25–27] and ischemia-related neovascularization [28] has been reported. It is also known that anti-VEGF treatments are of benefit in DR [29, 30]. VEGF is known to have pro-inflammatory actions [31, 32]. Furthermore, high glucose stimulates increased VEGF production [33, 34], suggesting that onset of diabetes is sufficient to trigger the initiation and progression of DR and implying that strict maintenance of normoglycemia is of paramount importance to prevent DR. Thus, strategies developed to prevent increase in the production of TNF-α, ICAM-1, VCAM, and VEGF and prevent leukocyte activation could be of benefit in preventing or arresting the progression of DR. In this context, the role of PUFAs and their anti-inflammatory metabolites in DR needs particular attention.

Vascular endothelial growth factor in diabetic retinopathy

Several studies have suggested that VEGF is the main factor of neovascularization in DR, though there could be a role for other yet to be identified growth factors. The VEGF is a potent endothelial-specific mitogen. A direct correlation between vitreal VEGF levels and severity of macular edema and retinopathy [28, 35] has been reported. Hyperglycemia is a potent stimulator of VEGF secretion [33, 34]. The VEGF inhibits the apoptosis of endothelial cells [36, 37] that leads to the generation of immature vascular structures that are fragile and hence bleed easily, which favors retinal detachment and consequent blindness. The role of VEGF in DR is supported by the observation that anti-VEGF therapies are able to arrest or slow the progress of DR [29, 30], though they are not always effective.

Several options to manage DR at present include: topical and systemic steroids, topical and oral non-steroidal anti-inflammatory agents, laser photocoagulation treatment, immunomodulators, intravitreal injection of triamcinolone, and pars plana vitrectomy [38]. In this context, it is interesting to note that the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial showed that (the ACCORD-EYE substudy) use of fenofibrate was associated with a significant reduction in the risk of progression of DR. These results are in support of the results of the previous Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, in which type 2 diabetes patients who were randomized to receive fenofibrate benefitted from a significantly lower incidence of laser treatment for retinopathy, progression of retinopathy or a composite measure of retinopathy outcomes. Thus, these two studies, ACCORD-EYE and FIELD, revealed that there is a place for fenofibrate for the prevention of retinopathy alongside intensive management of traditional risk factors, such as hyperglycemia and high blood pressure [38].

Despite these treatment options, DR tends to progress, causes considerable vision loss and morbidity, and affects quality of life. In view of this, development of newer therapeutic strategies is certainly needed.

Polyunsaturated fatty acids and their products in diabetic retinopathy

It is evident from the preceding discussion that methods designed to suppress pro-inflammatory IL-6, TNF-α, ICAM-1 and VCAM expression, inhibit VEGF production and protect retinal vascular endothelial cells and retinal neuronal cells could be of benefit in the prevention, arrest and/or progression of DR.

Several studies have shown that PUFAs, especially EPA and DHA, inhibit the production of both IL-6 and TNF-α and suppress the expression of ICAM-1 and VCAM [39, 40]. It was reported that these PUFAs suppress VEGF production [41, 42]. In mice, it was reported that hyperoxia-induced premature retinopathy can be inhibited by the n-3 PUFAs EPA and DHA but not by n-6 PUFAs [43]. It was noted that suppression of VEGF production and neangiogenesis and retinopathy could be correlated with increased formation of resolvins from EPA and DHA, emphasizing the beneficial action of n-3 PUFAs in the prevention and/or arrest of DR and similar conditions [44–46]. Our own study [47] revealed that both LA and AA inhibit high-glucose-induced retinal vascular endothelial damage. In an extension of this study, we noted that ALA, the precursor of EPA and DHA, suppressed high-glucose-induced VEGF secretion in streptozotocin-induced diabetic animals [48], implying that pathological VEGF secretion is inhibited by ALA, similar to EPA and DHA [41, 42]. In this study [48], we also observed a decrease in plasma brain-derived neurotrophic factor (BDNF) and an increase in IL-6 and VEGF levels in alloxan-induced diabetic rats that was inhibited by ALA treatment. This evidence supports the contention that n-3 PUFAs and their products are of benefit in DR-associated events. Since PUFAs form an important constituent of cell membranes and thus regulate cell membrane fluidity, the ability of these fatty acids to regulate cell membrane fluidity could be yet another mechanism by which they are of benefit in DR, partly by regulating hemorheology [49, 50]. In this context, it is interesting to note that PUFAs augment the production of BDNF, a neurotrophic factor that is needed for the survival of retinal neuronal cells [51, 52]. This could be yet another mechanism by which PUFAs protect reti-
nal neuronal cells from undergoing degeneration due to DR.

In conclusion, it is evident from the preceding discussion that DR is an inflammatory condition, as evidenced by enhanced levels of IL-6, TNF-α, and VEGF in the plasma and vitreal fluid, increased expression of ICAM-1 and VCAM and leukostasis and enhanced generation of ROS by infiltrating leukocytes (leukocytes infiltrating the retinal vascular endothelial cells) and decreased anti-oxidants. The involvement of the inflammatory pathway in DR is especially interesting in the light of the observation that obesity, hypertension, hyperlipidemias, and insulin resistance are also low-grade systemic inflammatory conditions [53–67]. This implies that changes similar to those seen in DR could be seen in hypertension (such as hypertensive retinopathy) and DR events could be exacerbated when diabetes is associated with obesity, hyperlipidemias, hypertension and other features of metabolic syndrome. This may also explain why obesity, hypertension and type 2 diabetes occur together, since all are inflammatory conditions [54–72], and the basic pathophysiology seems to be similar if not identical. This also raises the important question whether DR and similar retinal changes are likely to occur in other inflammatory conditions such as rheumatoid arthritis, lupus, and scleroderma [70–72]. Since alterations in essential fatty acid metabolism and eicosanoids are not uncommon in these inflammatory conditions [53, 60, 63, 73, 74], it may explain the relationship(s) that exists in these diseases in the form of coexistence, occurring in the same subject and similar retinal and other ocular manifestations. In view of this, it is imperative that careful examination of the retina and other ocular structures is called for in all these diseases despite the fact that outwardly there are not complaints or manifestations.

Though anti-VEGF therapies are reasonably beneficial in DR, many patients still do not respond adequately. This calls for additional studies and strategies to suppress local inflammation seen in DR in order to prevent, postpone and/or arrest DR. The retina is rich in n-3 PUFAs, suggesting that these fatty acids and their products play a significant role in the structural and functional integrity of retina. This implies that alterations in the levels and metabolism of PUFAs could trigger initiation and progression of DR and other related retinal diseases and associated angiogenic processes. Several studies have shown a decrease in the plasma levels of AA, EPA and DHA in both type 1 and type 2 diabetes mellitus, suggesting that there is a close association among various PUFAs and their products and diabetes mellitus. It is noteworthy that IL-6, TNF-α, VEGF and other growth factors activate phospholipase A2, resulting in the release of PUFAs from the cell membrane lipid pool of cells [80–83]. The released PUFAs, especially n-3 PUFAs, suppress the production of IL-6, TNF-α and VEGF, and inhibit activation of leukocytes [45, 46, 53, 63, 74]. These results can be interpreted to mean that one purpose of activation of PLA2 and release of PUFAs is to suppress inappropriate production of IL-6, TNF-α, VEGF and adhesion molecules and free radical generation by leukocytes. Thus, there appears to be negative feedback regulation exerted by PUFAs on pro-inflammatory molecules. Since DR is a pro-inflammatory condition, it is logical to suggest that PUFAs and their products could have a role in DR. The observation that PUFAs and their anti-inflammatory products such as lipoxins, resolvins and protectins suppress IL-6, TNF-α, VEGF and ROS production lends support to such a suggestion [45, 46]. The ability of PUFAs, lipoxins, resolvins and protectins to suppress IL-6, TNF-α and VEGF production and suppress free radical generation and restore anti-oxidant homeostasis both in vitro and in vivo is in line with such a concept [14, 46]. In view of this, it is imperative that in-depth studies are performed in future to delineate the role of PUFAs and their metabolites in DR and other retinopathies and exploit the knowledge gained to develop suitable therapeutic strategies. It is noteworthy that AA, EPA and DHA are also metabolized by cytochrome P450 enzymes to form various respective epoxyeicosatrienoic acids (EETs) that have potent anti-inflammatory actions [84, 85] (Figure 2). The possible role of these EETs and hydroxyeicosatetraenoic acids (HETEs) in DR also needs to be studied.

Future perspectives

Based on the preceding discussion, we suggest that it is essential to measure plasma and vitreal levels of PUFAs and their products and correlate the same to various stages of DR, response to therapy and progression of disease. Results of such studies may give clues as to when lipoxins and similar bioactive lipids could be used for the prevention and management of DR, either by themselves or their synthetic analogues could be exploited for this purpose.

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