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Long-Chain Polyunsaturated Fatty Acids and Age-Related Macular Degeneration

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Abstract

Age-related macular degeneration (AMD) is one of the leading causes of blindness worldwide. Long-chain and very long-chain polyunsaturated fatty acids (LC and VLC-PUFAs) have been linked to AMD pathogenesis through epidemiologic, biochemical, and genetic studies; however, the exact mechanisms of pathogenesis are unknown. Here, we review the scientific and clinical evidence supporting the role of PUFAs in AMD and discuss future directions for elucidating the roles of these fatty acids in AMD pathogenesis.

Keywords

Age-related macular degeneration (AMD); Long-chain polyunsaturated fatty acids (LC-PUFA); Elongation of very long-chain fatty acids; Lipids in the retina biology; PUFA in clinical trials for AMD

7.1 Introduction

Age is one of the most relevant clinical traits in predicting disease risk, mental and physical performance, mortality, and a number of other critical health issues. The average population age is anticipated to significantly increase in the next few decades what brings the wealth of interest in studying aging and improving quality of life in advanced age individuals. Changes in visual capability in later adulthood impact the ability to perform common everyday visual tasks and thus influence the quality of life and well-being. Therefore, it is not surprising that blindness and vision impairment are among the most feared medical conditions, right after cancer and cardiovascular disease. On a molecular level, aging is associated with a gradual decline in the efficiency and accuracy of molecular processes, including changes in metabolism, gene expression, and epigenetics, leading to a deterioration of cell functions.

Vision is one of the top predictors of aging. For example, visual contrast sensitivity score was among the top five individual predictors of age out of 377 evaluated variables (Swindell et al. 2010). Additionally, a number of eye diseases are age-related, with the most prevalent

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being age-related macular degeneration (AMD), which affects almost ten million individuals in the United States alone and is known to be the leading cause of blindness in industrialized nations (Luu and Palczewski 2018). AMD is a complex, late-onset human disease characterized by the formation of lipid-rich extracellular deposits called drusen, localized inflammation, and, ultimately, retinal degeneration in the macula. AMD is multifactorial, in that it has both genetic and environmental components (Crabb et al. 2002). There are two types of advanced AMD, an exudative "wet" from which results from abnormal neovascularization underneath the retina and leakage and a nonexudative "dry" form which results in gradual atrophy of the retinal pigment epithelium with concurrent photoreceptor loss. While exudative AMD is currently treated with inhibitors of vascular endothelial growth factor, there is yet no treatment to prevent progression of nonexudative AMD, as well as a dearth of animal models is available to study the disease. In this mini-review, we will discuss the role of polyunsaturated fatty acids (PUFAs) in retinal biology, biochemical and clinical evidence linking PUFAs to AMD, and future research directions to better understand the role of PUFAs in AMD pathogenesis.

7.2 LC-PUFAs and VLC-PUFAs in Retina Biology

Lipids play a crucial role in cell membrane integrity, cell signaling, and metabolism. A major class of lipids is polyunsaturated fatty acids (PUFAs), which are characterized by more than one double bond in their carbon backbone. PUFAs are divided into two major classes: omega-3 (n-3) or omega-6 (n-6) fatty acids, depending on whether the first double bond is on the third or sixth carbon from the terminal methyl group. PUFAs can synthesized from the essential fatty acids, linoleic acid and alpha-linoleic acid, through a biosynthesis pathway involving fatty acid desaturases and elongases to result in long-chain PUFAs (LC-PUFAs, defined as 18–22 carbons) such as docosahexaenoic acid (DHA) as well as very long-chain PUFAs (VLC-PUFAs; defined as greater than 22 carbons) (Fig. 7.1).

PUFAs are important components of the outer segments of retina photoreceptors and have been shown to interact with rhodopsin, suggesting their role in phototransduction. DHA is the major polyunsaturated fatty acid in the retina and brain. Its presence in the disk membrane of retinal photoreceptor outer segment is indispensable for retinal function and protects against damage from bright light and oxidative stress (Bazan et al. 2011). DHA accounts for 20–30% of the fatty acids in phosphatidylcholine (PC) or phosphatidylethanolamine (PE) of outer segment disk membranes. It has been also suggested that particularly VLC-PUFAs (>C26) are suited to build highly curved membranes in photoreceptor outer segment disks. Despite their importance and abundance in the retina, the exact function of PUFAs in the retina is still poorly understood.

During the process of daily renewal, photoreceptors are constantly shedding their outer segment membranes, which are phagocytosed by the RPE where PUFAs are recycled and further processed. For example, membrane-bound (n-3) and (n-6) PUFAs are cleaved by phospholipases A_1 and A_2, leading to metabolism by three major pathways, the cyclooxygenases (COX), lipoxygenases (LOX), and cytochrome P450 oxidases, resulting in metabolites with diverse functions. It has been shown that (n-3) PUFA metabolites such as prostaglandins have generally found to be anti-inflammatory, while (n-6) metabolites such as

PGE_2, TXA_2, and 5-hydroxyeicosatetranenoic acid have been found to be inflammatory (reviewed in Gong et al. (2017)). Additionally, during the process of daily recycling, DHA can serve as a precursor for neuroprotective docosanoids, while the release of longer PUFAs (>C30) can lead to the formation of elovanoids, yet another two classes of pro-homeostatic lipid mediators (Bazan 2018) (Fig. 7.1). This description is still an oversimplification.

Role of VLC-PUFAs in retina biology has been emphasized by the discovery of human mutations in the ELOVL4 gene, a key enzyme in the synthesis of VLC-PUFAS. This dominant negative mutation is associated with Stargardt-like macular dystrophy (STGD3) which shares pathological features with dry AMD including macular deposits (Bernstein et al. 2001; Edwards et al. 2001; Zhang et al. 2001), but it occurs at a young age (Agbaga et al. 2008; Harkewicz et al. 2012). Interestingly, although polymorphisms in other members of the VLC-PUFA synthesis pathway have been correlated with lower levels of PUFAs in the blood (Lemaitre et al. 2011), they have not been identified as risk factors for AMD.

Studies of VLC-PUFAs in human eyes have strengthened the relationship with VLC-PUFAs and AMD. Studies by Paul Bernstein's group have demonstrated that levels of DHA and other VLC-PUFAs, as well as the ratio of (n-3)/(n-6) VLC-PUFAs, were decreased in the retina and RPE-choroid of human AMD eyes compared to age-matched controls (Liu et al. 2010). These results were confirmed with a follow-up study with an independent cohort. Additionally, this follow-up study showed a significant correlation in retinal lipids and serum and RBC lipid levels, suggesting that serum or RBC lipids could potentially serve as a reliable surrogate of retinal PUFA levels (Christen et al. 2011).

7.3 Clinical Evidence Implicating Long-Chain Polyunsaturated Fatty Acids in Age-Related Macular Degeneration

Multiple epidemiologic studies, both retrospective as well as prospective, have suggested that diets high in (n-3)LC-PUFAs are associated with lower rates of age-related macular degeneration, with low dietary intake of (n-3) LC-PUFAs associated with higher risk of developing the disease (reviewed in Chong et al. (2008) and van Leeuwen et al. (2018)). In addition, two large studies demonstrated that high plasma levels of (n-3)LC-PUFAs were correlated with decreased risk of AMD (Christen et al. 2011; Merle et al. 2013). In the Age-Related Eye Disease Study (AREDS), a large prospective study investigating factors of progression to advanced AMD, subjects with the highest self-reported intake of foods rich in (n-3)LC-PUFAS were 30% less likely to develop central GA and 50% less likely to develop AMD than subjects with the lowest self-reported intake (Sangiovanni et al. 2009).

These studies linking omega-3 PUFAs to increased risk of AMD led to prospective studies to test whether omega-3 PUFA supplementation could lead to decreased progression of advanced AMD. Two large prospective randomized placebo-controlled studies, the AREDS2 study and the nutritional AMD study (NAT-2), examined the effect of (n-3) PUFA supplementation to prevent progression to advanced AMD or wet AMD. The AREDS2 study was a large prospective study consisting of over 4000 individuals to determine whether supplementation of DHA (650 mg/day) and EPA (350 mg/day) could prevent progression to advanced AMD beyond the original AREDS formulation. Five years of supplementation of

DHA and EPA did not reduce the risk of progression to advanced AMD beyond the original AREDS formation (Group et al. 2012). In another large prospective study, the NAT-2 study looked at oral supplementation of DHA to prevent wet AMD in patients with high risk of developing AMD. There was no significant difference between oral supplementation of DHA and placebo after 3 years in progression to wet AMD (Souied et al. 2013). How does one resolve the negative findings of the prospective AREDS2 and NAT-2 studies and the wealth of epidemiology data suggesting that (n-3)PUFAs are associated with decreased risk of AMD? One possibility is that patient characteristics of the AREDS2 patients and NAT-2 were slightly different than the previous studies, limiting the statistical power actually to detect a difference. It was noted that the progression to advanced AMD or wet AMD in the placebo group was less than expected in the AREDS2 patients and NAT-2 patients based on historical data (van Leeuwen et al. 2018). Additionally, 11% of the placebo group were taking omega-3 PUFAs on their own, and yet these individuals were still placed in the placebo group, again skewing the result toward the null hypothesis (Age-Related Eye Disease Study 2 Research Group et al. 2014). Another explanation is that there is a minimum of (n-3)PUFAs that are needed to prevent age-related macular degeneration, beyond which there is no benefit of increased supplementation. Finally, it is unclear how oral supplementation with DHA or EPA affects retinal PUFA levels, in particular, local levels in the photoreceptors and RPE. Therefore, while large prospective studies have not demonstrated that (n-3) PUFA supplementation has not demonstrated a decreased risk of AMD, whether some form of (n-3) PUFA supplementation could be useful to prevent progression of AMD is still open for debate. Similarly in the open-label study with (n-3) PUFA supplementation of 11 STDG3 patients, no significant beneficial effect has been observed; however, this study was limited by poor compliance with supplementation (Choi et al. 2018).

7.4 Future Directions

Despite the biochemical, epidemiologic, and genetic evidence implicating PUFAs in AMD, the molecular mechanisms by which LC and VLC-PUFAs are involved in drusen formation and AMD pathogenesis are still poorly understood. Most of the work has focused on DHA, which while important, still there is very little known about other specific (n-3) VLC-PUFAs and their specific roles. Even less is known about (n-6) PUFAs in retina biology. Dissecting the roles of specific PUFAs beyond DHA is of the highest importance to understand the complex and integral role PUFAs play in aging and retinal disease. This may involve specific genetic strategies to dissect roles of specific enzymes in the PUFA synthesis pathway, as well as suggests new supplementation strategies of specific PUFAs. Additionally, while most of the attention has been on the role of PUFA in photoreceptors, the role of these lipids in the RPE has been largely unexplored, and potential studies may yield important insights about how the disturbances in the homeostasis between these two cell types contribute to macular degeneration pathogenesis.

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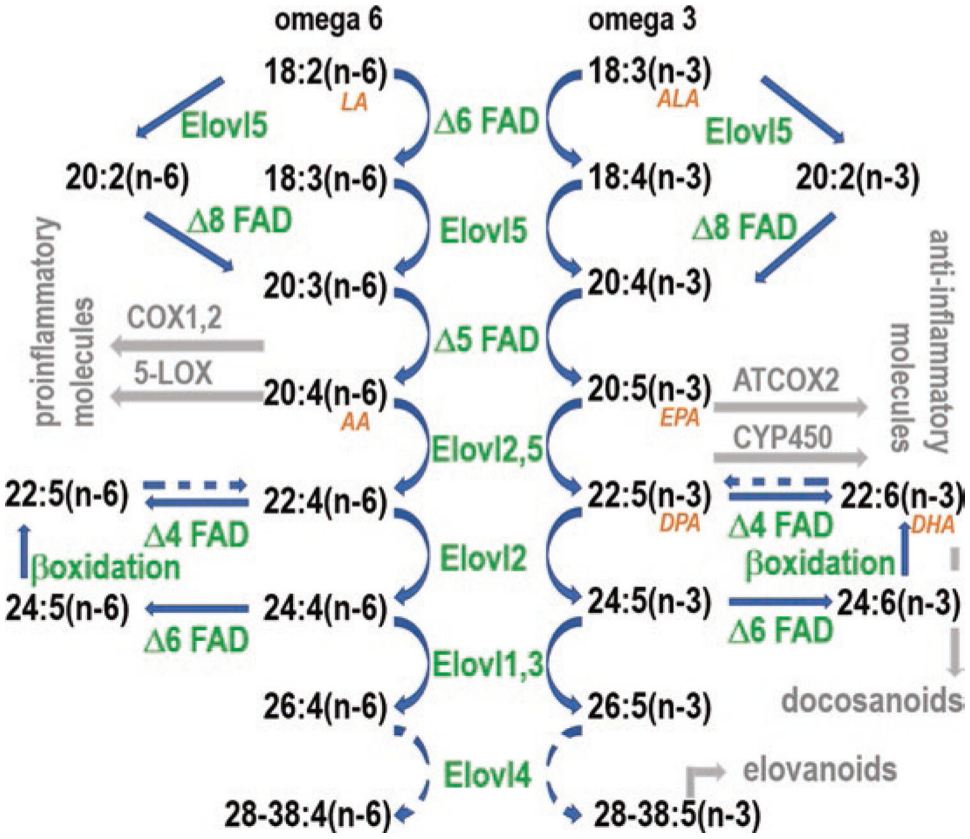

Fig. 7.1.

Omega-3 and omega-6 long-chain fatty acids synthesis pathways compete for the same enzymatic machinery in the cell. Several secondary products of the pathway play an important role in modulating cell homeostasis