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The role of omega-3 long-chain polyunsaturated fatty acids in health and disease of the retina

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Abstract

In this work we advance the hypothesis that omega-3 (ω-3) long-chain polyunsaturated fatty acids (LCPUFAs) exhibit cytoprotective and cytotherapeutic actions contributing to a number of anti-angiogenic and neuroprotective mechanisms within the retina. ω-3 LCPUFAs may modulate metabolic processes and attenuate effects of environmental exposures that activate molecules implicated in pathogenesis of vasoproliferative and neurodegenerative retinal diseases. These processes and exposures include ischemia, chronic light exposure, oxidative stress, inflammation, cellular signaling mechanisms, and aging. A number of bioactive molecules within the retina affect, and are effected by such conditions. These molecules operate within complex systems and include compounds classified as eicosanoids, angiogenic factors, matrix metalloproteinases, reactive oxygen species, cyclic nucleotides, neurotransmitters and neuromodulators, pro-inflammatory and immunoregulatory cytokines, and inflammatory phospholipids. We discuss the relationship of LCPUFAs with these bioactivators and bioactive compounds in the context of three blinding retinal diseases of public health significance that exhibit both vascular and neural pathology.

How is ω-3 LCPUFA status related to retinal structure and function? Docosahexaenoic acid (DHA), a major dietary ω-3 LCPUFA, is also a major structural lipid of retinal photoreceptor outer segment membranes. Biophysical and biochemical properties of DHA may affect photoreceptor membrane function by altering permeability, fluidity, thickness, and lipid phase properties. Tissue DHA status affects retinal cell signaling mechanisms involved in phototransduction. DHA may operate in signaling cascades to enhance activation of membrane-bound retinal proteins and may also be involved in rhodopsin regeneration. Tissue DHA insufficiency is associated with alterations in retinal function. Visual processing deficits have been ameliorated with DHA supplementation in some cases.

What evidence exists to suggest that LCPUFAs modulate factors and processes implicated in diseases of the vascular and neural retina? Tissue status of LCPUFAs is modifiable by and dependent upon dietary intake. Certain LCPUFAs are selectively accreted and efficiently conserved within the neural retina. On the most basic level, ω-3 LCPUFAs influence retinal cell gene expression, cellular differentiation, and cellular survival. DHA activates a number of nuclear hormone receptors that operate as transcription factors for molecules that modulate reduction-oxidation-sensitive and proinflammatory genes; these include the peroxisome proliferator-activated receptor-α (PPAR-α) and the retinoid X receptor. In the case of PPAR-α, this action is thought to prevent endothelial cell dysfunction and vascular remodeling through inhibition of: vascular smooth muscle cell proliferation, inducible

Abbreviations: A2E, *N*-retinylidene-*N*-retinylethanolamine; AA, arachidonic acid (20:4ω-6); AMD, age-related macular degeneration; ARM, age-related maculopathy; COX, cyclooxygenase; DHA, docosahexaenoic acid (22:6ω-3); DPA, docosapentaenoic acid; DR, diabetic retinopathy; EFA, essential fatty acid; EPA, eicosapentaenoic acid (20:5ω-3); GA, geographic atrophy; HETE, hydroxyeicosatetraenoic acid; HPETE, hydroperoxyeicosatetraenoic acid; HUVEC, human umbilical vein endothelial cell; ICAM, intracellular cell adhesion molecule; IFN, interferon; Ig, immunoglobulin; IL, interleukin; IPM, interphotoreceptor matrix; LA, linoleic acid (18:2ω-6); LCPUFA, long-chain polyunsaturated fatty acid; LOX, lipoxygenase; LT, leukotriene; NFκB, nuclear-factor kappa B; NPDR, non-proliferative diabetic retinopathy; NV, neovascular; PAF, platelet-activating factor; PC, phosphatidylcholine; PDR, proliferative diabetic retinopathy; PEA, phosphatidylethanolamine; PG, prostaglandin; PI, phosphatidylinositol; PKC, protein kinase C; PLA_2, phospholipase A_2; PPAR, peroxisome proliferator-activated receptor; PS, phosphatidylserine; redox, oxidation-reduction; ROP, retinopathy of prematurity; RPE, retinal pigment epithelium; RXR, retinoid X receptor; TNF, tumor necrosis factor; TX, thromboxane; uPA, urokinase-type plasminogen activator; VEGF, vascular endothelial growth factor; α-LLNA, α-linolenic acid (18:3ω-3)

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nitric oxide synthase production, interleukin-1 induced cyclooxygenase (COX)-2 production, and thrombin-induced endothelin 1 production.

Research on model systems demonstrates that ω-3 LCPUFAs also have the capacity to affect production and activation of angiogenic growth factors, arachidonic acid (AA)-based vasoregulatory eicosanoids, and MMPs. Eicosapentaenoic acid (EPA), a substrate for DHA, is the parent fatty acid for a family of eicosanoids that have the potential to affect AA-derived eicosanoids implicated in abnormal retinal neovascularization, vascular permeability, and inflammation. EPA depresses vascular endothelial growth factor (VEGF)—specific tyrosine kinase receptor activation and expression. VEGF plays an essential role in induction of: endothelial cell migration and proliferation, microvascular permeability, endothelial cell release of metalloproteinases and interstitial collagenases, and endothelial cell tube formation. The mechanism of VEGF receptor down-regulation is believed to occur at the tyrosine kinase nuclear factor-kappa B (NFκB). NFκB is a nuclear transcription factor that up-regulates COX-2 expression, intracellular adhesion molecule, thrombin, and nitric oxide synthase. All four factors are associated with vascular instability. COX-2 drives conversion of AA to a number angiogenic and proinflammatory eicosanoids. Our general conclusion is that there is consistent evidence to suggest that ω-3 LCPUFAs may act in a protective role against ischemia-, light-, oxygen-, inflammatory-, and age-associated pathology of the vascular and neural retina.
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