Pharmacological Research 70 (2013) 13–19

Contents lists available at SciVerse ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Invited review

DHA supplementation: Current implications in pregnancy and childhood

Lynette K. Rogers[a,b,*], Christina J. Valentine[c], Sarah A. Keim[a,b,d]

[a] The Research Institute at Nationwide Children's Hospital, United States
[b] Department of Pediatrics, The Ohio State University, United States
[c] Cincinnati Children's Hospital, United States
[d] Division of Epidemiology, The Ohio State University, United States

ARTICLE INFO

Article history:
Received 30 May 2012
Received in revised form 7 November 2012
Accepted 10 December 2012

Keywords:
DHA
Long chain fatty acids
Natural products
Lipids
Omega-3

ABSTRACT

Dietary supplementation with ω-3 long chain fatty acids including docosahexaenoic acid (DHA) has increased in popularity in recent years and adequate DHA supplementation during pregnancy and early childhood is of clinical importance. Some evidence has been built for the neuro-cognitive benefits of supplementation with long chain polyunsaturated fatty acids (LCPUFA) such as DHA during pregnancy; however, recent data indicate that the anti-inflammatory properties may be of at least equal significance. Adequate DHA availability in the fetus/infant optimizes brain and retinal maturation in part by influencing neurotransmitter pathways. The anti-inflammatory properties of LCPUFA are largely mediated through modulation of signaling either directly through binding to receptors or through changes in lipid raft formation and receptor presentation. Our goal is to review the current findings on DHA supplementation, specifically in pregnancy and infant neurodevelopment, as a pharmacologic agent with both preventative and therapeutic value. Given the overall benefits of DHA, maternal and infant supplementation may improve neurological outcomes especially in vulernable populations. However, optimal composition of the supplement and dosing and treatment strategies still need to be determined to lend support for routine supplementation.

Contents

1. Introduction

The therapeutic value of long chain polyunsaturated fatty acids (LCPUFA) was appreciated by the early 1980s when epidemiologic data indicated that populations consuming large quantities of cold water fish had lower incidences of inflammatory diseases [1–3]. Furthermore, cold water fish such as salmon, tuna, mackerel, and sardines contain substantial quantities of omega (ω)-3 LCPUFA. In the average Western diet, intake of fish containing high levels of (ω)-3 PUFA is limited and estimates are that only approximately

Abbreviations: DHA, docosahexaenoic acid; LCPUFA, long chain polyunsaturated fatty acids; TLR, toll like receptor; GPR, G-coupled protein receptor; PPARγ, peroxisome proliferator activated receptor-γ; MAPK, mitogen activated protein kinase; NFkB, nuclear factor kappaB; NPD1, neuroprotectin D1; RvE, resolvin E; RvD, resolvin D; IL, interleukin; TNFα, tumor necrosis factor α.

* Corresponding author at: Center for Perinatal Research, The Research Institute at Nationwide Children's Hospital, 700 Children's Dr., Department of Pediatrics, The Ohio State University, Columbus, OH, United States. Tel.: +1 614 355 6715; fax: +1 614 355 3455.
E-mail address: Lynette.Rogers@NationwideChildrens.org (L.K. Rogers).

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http://dx.doi.org/10.1016/j.phrs.2012.12.003

100 mg DHA + EPA/day are ingested by average adults in the United States [4].

Anthropologic data indicate that the evolution of modern man coincides with the migration of *Homo sapiens* to the waterways and the inclusion of marine foods in the diet [5]. These findings further coincide with the presence of DHA in neuronal tissues specifically at neural synapses and in the retina. The agricultural and industrial revolutions and the domestication of livestock and poultry have shifted mankind away from a diet rich in seafood and toward a diet high in saturated fats. This shift led to a relative disproportion in ω-6 to ω-3 fatty acids (originally 1–2:1; currently 10–20:1) and the predominance of ω-6 fatty acids [6].

Much of the US population (40–60%) has turned to complementary or alternative medicine to treat inflammation-based disease as well as promote health and well-being [7]. Of these alternative therapies, ω-3 LCPUFAs have received the attention of both the scientific and medical communities. Much information is available on the mechanistic actions of DHA as well as therapeutic value of DHA in improving pregnancy outcomes and enhancing infant neurodevelopment, especially in the context of prematurity (reviewed in [8–10]). However, significance and thus clinical implementation of the collective findings related to DHA therapy to improve neurodevelopmental outcomes and to attenuate inflammation in newborn infants and children have been hindered by the lack of standardization. Specifically the use of DHA alone or with other lipids and a broad range of doses have been reported, as well as varying measures of the outcomes of interest [11,12].

2. Mechanisms of action

DHA is metabolically active and has been the focus of numerous studies in nutrition, neurodevelopment, and immunology [8,10,13–16]. Although the mechanisms involved are not completely understood, the active properties of DHA are thought to include effects on neuronal development and plasticity, receptor-mediated signaling, changes in membrane fluidity, the formation of second messengers, and/or enhancement of the production of anti-inflammatory lipid mediators due to the availability of DHA as substrate [8,14,16] (Fig. 1).

2.1. Receptors

DHA has been shown to interact with several receptors, functioning as either an agonist or an antagonist in signaling responses. These receptors include plasma membrane bound Toll-like receptors (TLR) [17], the G-coupled protein receptor (GPR)120 [18], and the nuclear receptor peroxisome proliferator activated receptor gamma (PPARγ) [19]. In addition, animal studies have linked the need for LCPUFAs, specifically DHA, to dopamine and serotonin production, the activity of the respective receptors, and the presence of second messengers to facilitate neurotransmission [20–22]. Human studies have found decreased dopaminergic responses in infants that are LCPUFA deficit [23].

TLRs are key pattern recognition receptors that play a significant role in innate and adaptive immune responses [24]. Ligand binding to TLR2 and 4 activates downstream pathways that include the mitogen activated protein kinases (MAPK) and NFkB resulting in the promotion of inflammatory responses [17]. TLRs are highly expressed on microglia and mediate the expression of cytokines in the developing brain specifically in the context of inflammation (reviewed in Ref. [25]). In addition, endogenous compounds such as saturated fatty acids can mediate sterile inflammation through activating TLRs, one explanation for the chronic inflammation observed in obesity [26]. LCPUFAs have been shown to interfere with TLR activation directly inhibiting dimerization and activation of both TLR-2 and -4, thus blocking inflammatory signaling cascades [26].

Recently, investigations have identified GPRs that are activated by fatty acids. Specifically, GPR120 is highly expressed on pro-inflammatory macrophages, interacts with DHA, and can modulate anti-inflammatory pathways [18]. Oh et al. demonstrated that activation of GPR120 in macrophages and adipocytes by DHA did not involve Gαq proteins but rather required the recruitment of β-arrestin 2 into a complex that prevented the phosphorylation of transforming growth factor-β activated kinase 1 [18]. This

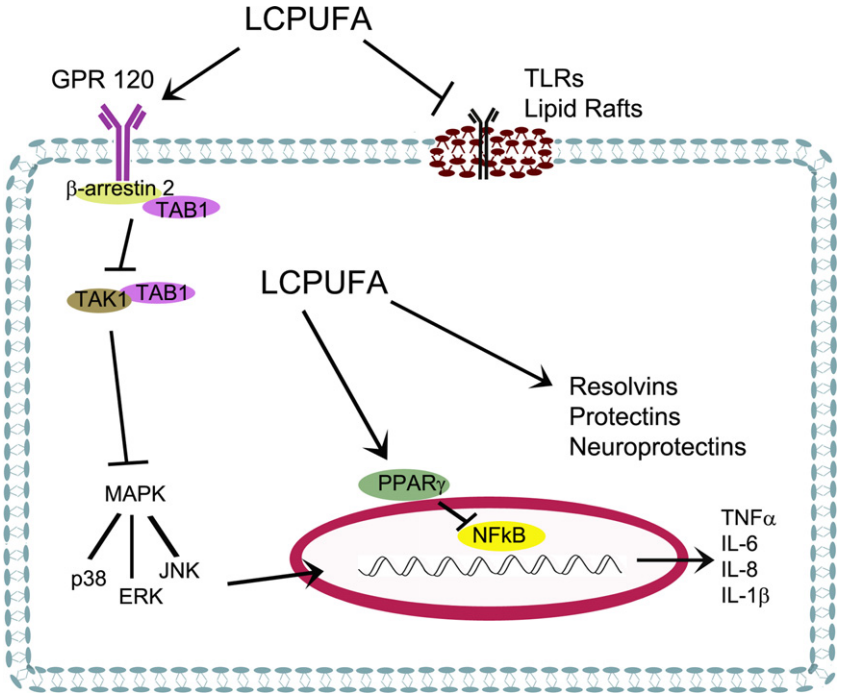

Fig. 1. LCPUFAs can modulate inflammation through several pathways. These pathways include agonism or antagonism of receptors such as TLRs, GPR120, and PPARγ as well as providing substrate for the production of pro-resolution lipid metabolites.