Journal of Cardiology 67 (2016) 22–27

Contents lists available at ScienceDirect

Journal of Cardiology

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

Review

Cardioprotective mechanism of omega-3 polyunsaturated fatty acids

Jin Endo (MD, PhD)[a,*], Makoto Arita (PhD)[b,c,**]

[a] Department of Cardiology, Keio University School of Medicine, Tokyo, Japan
[b] Laboratory for Metabolomics, RIKEN Center for Integrative Medical Sciences, Kanagawa, Japan
[c] Graduate School of Medical Life Science, Yokohama City University, Kanagawa, Japan

ARTICLE INFO

Article history:
Received 31 July 2015
Accepted 31 July 2015
Available online 8 September 2015

Keywords:
Omega-3 polyunsaturated fatty acids
Cardiovascular disease
Anti-inflammation
Specialized proresolving mediators
18-Hydroxyeicosapentaenoic acid

ABSTRACT

Omega-3 polyunsaturated fatty acids (PUFAs), such as eicosapentaenoic acid and docosahexaenoic acid, are widely regarded as cardioprotective. Several large-scale, randomized clinical trials have shown that dietary intake of omega-3 PUFAs improves the prognosis of patients with symptomatic heart failure or recent myocardial infarction. Therefore, dietary consumption of omega-3 PUFA is recommended in international guidelines for the general population to prevent the occurrence of cardiovascular diseases (CVDs). However, the precise mechanisms underlying the cardioprotective effects of omega-3 PUFAs are not fully understood. Omega-3 PUFAs can be incorporated into the phospholipid bilayer of cell membranes and can affect membrane fluidity, lipid microdomain formation, and signaling across membranes. Omega-3 PUFAs also modulate the function of membrane ion channels, such as Na and L-type Ca channels, to prevent lethal arrhythmias. Moreover, omega-3 PUFAs also prevent the conversion of arachidonic acid into pro-inflammatory eicosanoids by serving as an alternative substrate for cyclooxygenase or lipoxygenase, resulting in the production of less potent products. In addition, a number of enzymatically oxygenated metabolites derived from omega-3 PUFAs were recently identified as anti-inflammatory mediators. These omega-3 metabolites may contribute to the beneficial effects against CVDs that are attributed to omega-3 PUFAs.

© 2015 Japanese College of Cardiology. Published by Elsevier Ltd. All rights reserved.

Contents

Introduction

The beneficial effects of n-3 polyunsaturated fatty acids (PUFAs), primarily eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), were first recognized in the late 1960s when epidemiological evidence from the Inuit population, who consume an n-3 PUFA-rich diet, showed that they have a low incidence of myocardial infarction [1]. Subsequently, a large number

* Corresponding author at: Department of Cardiology, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan. Tel.: +81 3 5363 3874; fax: +81 3 5363 3875.
** Corresponding author at: Laboratory for Metabolomics, RIKEN Center for Integrative Medical Sciences (IMS), 1-7-22 Suehiro-cho, Tsurumi-ku, Yokohama City, Kanagawa 230-0045, Japan. Tel.: +81 45 503 7055; fax: +045 503 7054.
E-mail addresses: jinendo@keio.jp (J. Endo), makoto.arita@riken.jp (M. Arita).

http://dx.doi.org/10.1016/j.jjcc.2015.08.002
0914-5087/© 2015 Japanese College of Cardiology. Published by Elsevier Ltd. All rights reserved.

of randomized clinical trials have investigated the efficacy of supplementation with fish oil or omega-3 PUFAs. The GISSI-Prevenzione trial [2] was the first large-scale, randomized trial to provide evidence that dietary supplementation with omega-3 PUFAs had favorable effects on hard clinical end-points in post-myocardial infarction patients. The GISSI-HF trial [3] also showed that omega-3 PUFAs could reduce morbidity and mortality in patients with symptomatic chronic heart failure who were receiving standard treatments, including aspirin, beta-blockers, angiotensin-converting enzyme inhibitor/angiotensin receptor blockers, and aldosterone receptor blockers. Further, the JELIS study [4], a randomized large trial conducted in Japan, revealed that treatment with a pharmaceutical preparation of highly purified EPA in addition to statin significantly prevented cardiovascular events in patients with recent myocardial infarction through an apparently cholesterol-independent mechanism. The results of the above-mentioned studies showed that omega-3 PUFA treatment is safe and well tolerated, and the clinical improvements observed were additive to those of other well-established therapies. Therefore, in a scientific statement from the American Heart Association, the consumption of >1 g/day of omega-3 PUFAs (EPA+DHA; this dose was largely determined from the results of the GISSI-Prevenzione study) was recommended for patients with coronary artery disease to reduce triglyceride (TG) levels, maintain cardiac function, and reduce the risk of coronary heart disease [5]. In addition, many animal studies have demonstrated that omega-3 PUFAs have pleiotropic beneficial effects in the cardiovascular system, including anti-arrhythmic, plasma TG-lowering, anti-thrombotic, anti-atherosclerotic, endothelial relaxation, blood pressure-lowering, anti-inflammatory, and anti-fibrotic effects [6]. In this review, we present recent advances in our understanding of the molecular mechanisms underlying the cardioprotective effects of omega-3 PUFAs.

Modification of the cell membrane milieu by incorporation of omega-3 PUFAs

The cell membrane is composed of phospholipids (PLs) that contain various types of fatty acids. The length and saturation of the fatty acids in these PLs is thought to affect the properties of cell membranes by altering the microdomain "rafts" and "caveolae" that concentrate membrane proteins and lipids and function as signaling platforms. Since omega-3 PUFAs have many double bonds and long-chain carbons, their incorporation into the PLs within a membrane can alter its properties and influence the function of various membrane proteins (Fig. 1), including the suppression of protein kinase C theta signaling and interleukin (IL)-2 production [7], and the disruption of dimerization and recruitment of toll-like receptor 4 [8]. Of note, alteration of the lipid microenvironment in cardiomyocytes through the inclusion of omega-3 PUFAs can modulate ion channel function, leading to anti-arrhythmic effects [6].

Anti-arrhythmic effects of omega-3 PUFAs due to ion channel modulation

The clinical outcomes of several trials, including GISSI-Prevenzione, have suggested that omega-3 PUFAs might prevent the occurrence of sudden cardiac death triggered by lethal arrhythmias. Accumulating evidence from in vivo and in vitro experiments has demonstrated that omega-3 PUFAs exert anti-arrhythmic effects through modulation of myocyte electrophysiology. Omega-3 PUFAs reduce the activity of membrane sodium channels in cardiomyocytes, thus increasing the threshold for membrane potential depolarization [9]. EPA and DHA also modulate the activity of L-type calcium channels, leading to a reduction in free cytosolic calcium ion, which stabilizes myocyte

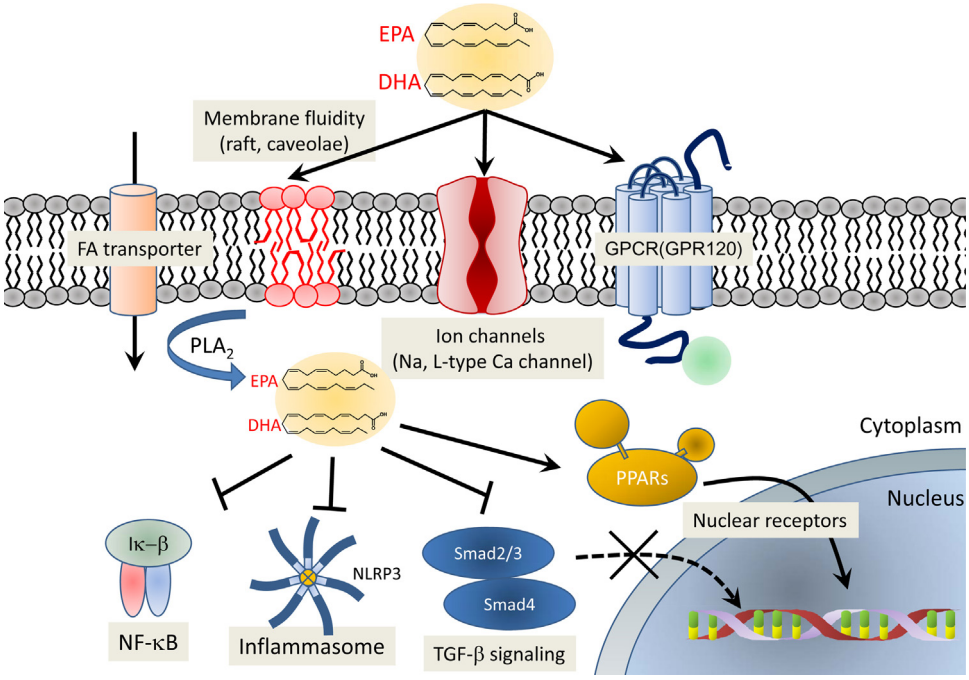

Fig. 1. ***The proposed molecular mechanism of cardioprotection by omega-3 PUFAs.*** Omega-3 PUFAs modulate cell membrane property when incorporated into the phospholipid bilayer and control membrane ion channels to prevent lethal arrhythmia. Also omega-3 PUFAs exert anti-inflammatory and anti-fibrotic effects by modifying NF-κB signaling, the NLRP3 inflammasome, PPARα/γ, GPR120, and TGF-β signaling.
NF-κB: nuclear factor-κB; NLRP3: NOD-like receptor family, pyrin domain containing 3; PPARα/γ: peroxisome proliferator-activated receptor α/γ; GPR120: G protein-coupled receptor 120; TGF-β: transforming growth factor-β.

Download English Version:

https://daneshyari.com/en/article/2962898

Download Persian Version:

https://daneshyari.com/article/2962898

Daneshyari.com