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Lipoxins, Resolvins, Protectins, Maresins, and Nitrolipids: Connecting Lipids, Inflammation, and Cardiovascular Disease Risk

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Abstract Essential fatty acids and their metabolites (γ-linolenic acid [GLA], dihomo-GLA, arachidonic acid, eicosapentaenoic acid, and docosahexaenoic acid; prostaglandin E_1; prostacyclin [PGI_2]; PGI_3; lipoxins; resolvins; protectins; maresins; and nitrolipids) prevent platelet aggregation, produce vascular relaxation, inhibit neutrophil degranulation and superoxide formation, inhibit platelet activation, possess peroxisome proliferator-activated receptor-γ ligand activity, and release nitric oxide. Thus, they lower blood pressure, are anti-arrhythmic and anti-inflammatory in nature, reduce low-density lipoprotein cholesterol, ameliorate the adverse actions of homocysteine, activate telomerase, and have cytoprotective properties—actions that prevent atherosclerosis and cardiovascular disease. Because coronary heart disease (CHD) and atherosclerosis are low-grade systemic inflammatory conditions, it is likely that reduced formation of lipoxins, resolvins, protectins, maresins, and nitrolipids plays a significant role in the pathogenesis of CHD. Hence, development of stable synthetic analogues of lipoxins, resolvins, protectins, and maresins may form a new therapeutic approach to CHD and other low-grade systemic inflammatory conditions.

Keywords Coronary heart disease · Polyunsaturated fatty acids · Lipoxins · Resolvins · Maresins · Protectins · Nitrolipids · Platelets · Atherosclerosis

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Introduction

Dyslipidemia, diabetes mellitus, hypertension, and obesity are important risk factors for coronary heart disease (CHD). Smoking cessation, β-blockers, anti-platelet agents, angiotensin-converting enzyme (ACE) inhibitors, and lipid-lowering agents such as statins reduce the risk of vascular events to a moderate but important degree [1]. But these medicines are not without significant side effects.

We and others observed that in CHD, hypertension, diabetes mellitus, hyperlipidemias, and obesity, essential fatty acid (EFA) metabolism is abnormal such that plasma phospholipid concentrations of arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) are low [2–6, 7••]. Despite the fact that deficiency of polyunsaturated fatty acids (PUFAs) is present in CHD, hypertension, diabetes, hyperlipidemias, and obesity, and increased intake of PUFAs is of benefit in these diseases, exact mechanism(s) of their protective action remained unexplained.

Low-Grade Systemic Inflammation Occurs in CHD

CHD is a low-grade systemic inflammatory condition because these subjects have enhanced plasma levels of reactive oxygen species (ROS), C-reactive protein (CRP), interleukin (IL)-6, and tumor necrosis factor (TNF)-α, and low circulating levels of endothelial nitric oxide (NO) and various PUFAs [8•]. Increased ROS decreases anti-oxidant content of the cells/tissues. This leads to an imbalance between the pro- and anti-oxidant molecules that favor tissue damage in CHD [8•]. Hence, it is important that adequate cytoprotective and anti-oxidant defenses are available in the cells/tissues to protect them against excess pro-oxidants.

Balance Between Pro- and Anti-Oxidant Defenses in CHD

Hs-CRP, lipoprotein-associated phospholipase A_2 (Lp-PLA_2), proinflammatory cytokines, ROS, and myeloperoxidase (MPO) have potent cytotoxic actions and are increased in patients with CHD and atherosclerosis. To protect themselves from these cytotoxic molecules, cells/tissues should have adequate amounts of superoxide dismutase, vitamin E, catalase, and glutathione group of anti-oxidants. But these are not always sufficient to protect tissues from the cytotoxic action of ROS and MPO. In this context, lipid-soluble molecules such as lipoxins (LXs), resolvins, protectins, maresins, and nitrolipids that are derived from the ubiquitous PUFAs deserve special attention. LXs, resolvins, protectins, and maresins possess cytoprotective and cardioprotective actions, by virtue of their ability to inhibit production of IL-6 and TNF-α, suppress free radical generation, and enhance tissue repair [7••, 8•]. When EPA, DHA, AA, and aspirin are administered in adequate amounts, LXs, resolvins, protectins, maresins, and nitrolipids are formed that prevent myocardial damage. This explains the beneficial actions of EPA/DHA/AA and aspirin in both primary and secondary prevention of CHD.

This implies that deficiency of PUFAs seen in CHD leads to reduced formation of NO, LXs, resolvins, protectins, maresins, and nitrolipids that would initiate atherosclerosis and CHD and/or worsen the existing disease. Based on this evidence, it is predicted that plasma levels of hs-CRP, ROS, MPO, Lp-PLA_2, and LP will be increased, whereas those of LXs, resolvins, protectins, maresins, and nitrolipids are decreased in patients with CHD. Furthermore, a balance between these pro- and anti-inflammatory molecules may aid in predicting prognosis of CHD [9••]. For instance, subjects with low levels of LXs, resolvins, protectins, maresins, and nitrolipids may have poor outcome and higher incidence of cardiac failure, arrhythmias, and recurrence of myocardial infarction. Statins and thiazolidinediones enhance the formation of myocardial 15-epi-LXA_4 and EFAs mediate some of their actions, which could explain the ability of statins and glitazones to prevent CHD [10–13]. This implies that those who have low levels of EFAs and their metabolites could be resistant to the beneficial action of statins and glitazones; such subjects will benefit from supplementation of AA/EPA/DHA.

Metabolism of EFAs

EFAs, which are needed for survival, cannot be synthesized in the body and hence have to be obtained in our diet; thus, they are essential [6–9••]. There are two types of naturally occurring EFAs in the body: the omega (n)-6 series derived from linoleic acid (LA; 18:2), and the n-3 series derived from α-linolenic acid (ALA; 18:3). Both n-6 and n-3 series are metabolized by the same set of enzymes to their respective long-chain metabolites.

LA is converted to γ-linolenic acid (GLA; 18:3, n-6) by the action of the enzyme Δ^6 desaturase (d-6-d), and GLA is elongated to form dihomo-GLA (DGLA; 20:3, n-6), the precursor of the 1 series of prostaglandins (PGs). DGLA can also be converted to AA (20:4, n-6) by the action of the enzyme Δ^5 desaturase (d-5-d). AA forms the precursor of the 2 series of PGs, thromboxanes, and the 4 series of leukotrienes (LTs). ALA is converted to EPA (20:5, n-3) by d-6-d and d-5-d. EPA forms the precursor of the 3 series of PGs and the 5 series of LTs (Fig. 1). AA and EPA give rise to their respective hydroxy acids, which, in turn, are converted to respective LTs. In addition, AA, EPA, and DHA form precursor to anti-inflammatory compounds LXs, resolvins, protectins (neuroprotectin D_1 is one such compound derived from DHA), and maresins [6–9••, 12–14••]. PGs, LTs, LXs, and resolvins are highly active, modulate inflammation, and are involved in several physiologic and pathologic processes. Although the terms *EFAs* and *PUFAs* are used interchangeably, it should be understood that all EFAs are PUFAs but all PUFAs are not EFAs. Only LA and ALA qualify to be EFAs, whereas GLA, DGLA, AA, EPA, and DHA are PUFAs. LA, GLA, DGLA, AA, ALA, EPA, and DHA are also called LCPUFAs (long-chain PUFAs). In general, many authors use the terms *EFAs* and *PUFAs* interchangeably. This convention is followed in the present discussion.

Factors Influencing the Metabolism of EFAs

Dietary LA and ALA compete with one another for the same set of enzymes, and Δ^6 and Δ^5 desaturases prefer n-3 to n-6. Oleic acid (OA; n-9) that is not an EFA is also metabolized by the same desaturases. But, in view of the preference of these enzymes to LA and ALA, under normal physiologic conditions, the metabolites of n-9 are formed only in trivial amounts. Hence, presence of significant amounts of 20:3 n-9, a metabolite of OA, in the cells and plasma indicates EFA deficiency.

Of several factors that influence the activities of desaturases and elongases, saturated fats, cholesterol, trans-fatty acids, alcohol, adrenaline, and glucocorticoids inhibit Δ^6 and Δ^5 desaturases. Pyridoxine, zinc, and magnesium are necessary co-factors for normal Δ^6 desaturase activity. Insulin activates Δ^6 desaturase, whereas diabetics have reduced Δ^6 desaturase activity. The activity of Δ^6 desaturase decreases with age. Oncogenic viruses and radiation inhibit Δ^6 desaturase. Total fasting, protein deficiency, and glucose-rich diets reduce the activity of Δ^6 desaturase. A fat-free diet and partial caloric restriction enhances Δ^6 desaturase. Activities of Δ^6 and Δ^5 desaturases are decreased in diabetes

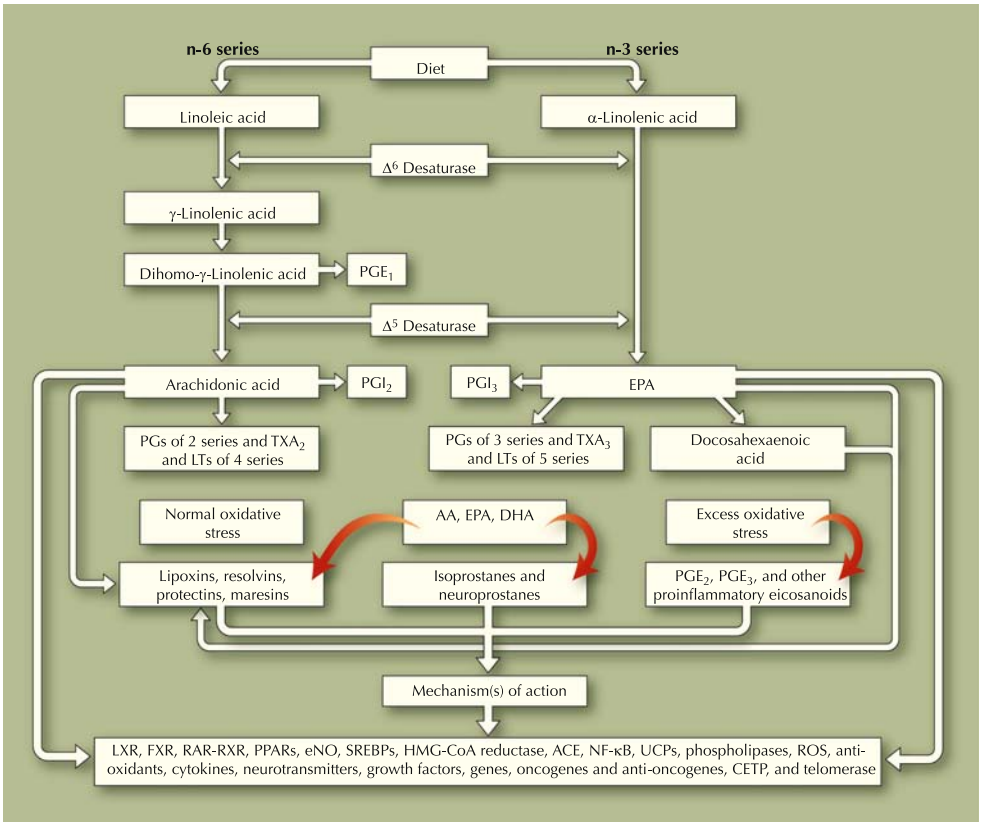

Fig. 1 Schematic showing the metabolism of essential fatty acids, their action on various enzymes, and factors that account for their beneficial actions in coronary heart disease. AA—arachidonic acid; ACE—angiotensin-converting enzyme; CETP—cholesteryl ester transfer protein; DHA—docosahexaenoic acid; eNO—endothelial nitric oxide; EPA—eicosapentaenoic acid; FXR—farnesoid X receptor; LT—leukotriene; LXR—liver X receptor; NF—nuclear factor; PG—prostaglandin; PPAR—peroxisome proliferator—activated receptor; RAR-RXR—retinoic acid receptor-retinoid X receptor; ROS—reactive oxygen species; SREBP—sterol regulatory element-binding protein; TXA_3—thromboxane A_3; UCP—uncoupling protein

mellitus, hypertension, hyperlipidemia, and metabolic syndrome. Trans- and saturated fatty acids, and cholesterol, interfere with EFA metabolism and promote inflammation, atherosclerosis, and CHD. This implies that trans-fats, saturated fats, and cholesterol have proinflammatory actions, whereas EFAs and PUFAs possess anti-inflammatory properties. The ability of trans-fats, saturated fats, and cholesterol to interfere with the formation of AA, EPA, and DHA from dietary LA and ALA could lead to decreased formation of LXs, resolvins, PGI_2 (prostacyclin), PGI_3, and other beneficial eicosanoids that prevent platelet aggregation, and leukocyte chemotaxis and activation. LXs, resolvins, protectins, and maresins decrease the formation of proinflammatory cytokines and produce vasodilatation, events that prevent or arrest atherosclerosis. In contrast, trans-fats, saturated fats, and cholesterol may directly activate leukocytes, induce the generation of free radicals, and enhance the production and release of proinflammatory cytokines that facilitate atherosclerosis. Trans-fats, saturated fats, and cholesterol may directly activate leukocytes and macrophages to enhance their ability to produce free radicals and proinflammatory cytokines. It is possible that trans-fats, saturated fats, and cholesterol may inhibit the formation of LXs, resolvins, protectins, maresins, PGI_2, and PGI_3. Thus, EFAs, especially EPA and DHA, are cytoprotective to endothelial cells, whereas trans-fats, saturated fats, and cholesterol produce endothelial dysfunction. AA, EPA, and DHA augment NO generation from endothelial cells and thus prevent endothelial dysfunction. In contrast, trans-fats, saturated fats, and cholesterol produce endothelial dysfunction and thus inhibit endothelial NO (eNO) production. Furthermore, NO quenches superoxide anion and thus prevents the cytotoxic action of superoxide anion and protects endothelial cells from free radical-induced damage. This implies that endothelial cells need adequate amounts of AA, EPA, and DHA so that they can generate physiologic amounts of eNO not only to prevent pathologic platelet aggregation and atherosclerosis but also to protect themselves from the cytotoxic actions of free radicals [2–4, 7••–9••].

NO reacts with PUFAs to yield their respective nitroalkene derivatives that can be detected in plasma. These nitroalkene derivatives, termed *nitrolipids*, produce vascular relaxation, inhibit neutrophil degranulation and superoxide formation, inhibit platelet activation, and show anti-atherosclerotic properties [2–4, 7••–9••, 15•].

PUFAs Modulate HMG-CoA Reductase and ACE Enzymes, and Possess Anti-arrhythmic, Anti-hypertensive, Anti-atherosclerotic, Anti-inflammatory, Cytoprotective, and Cardioprotective Actions

PUFAs inhibit HMG-CoA reductase enzyme similar to statins and hence are useful in the treatment of hyper-

lipidemias [11]. In fact, statins and PUFAs have many overlap actions that suggest that PUFAs mediate many, if not all, actions of statins [11], and this could be one mechanism by which they lower cholesterol levels. Recent studies revealed that statins augment concentrations of LXs in the heart [12, 13], lending support to this concept. Furthermore, when a combination of statins and PUFAs was administered, a synergistic beneficial effect was seen in patients with combined hyperlipemia [16].

Several studies suggested that PUFAs have modulatory influence on renin secretion and action, yet at times are independent of both renin secretion and PG formation [17, 18]. Because the anti-hypertensive actions of PUFAs seem to be independent of formation of PGs, it is likely that fatty acids themselves are able to bring about this action. Alternatively, LXs, resolvins, protectins, and maresins formed from various PUFAs possibly have anti-hypertensive action by inhibiting the ACE activity. But this proposal needs to be verified and confirmed.

Previously, I showed that PUFAs inhibit leukocyte ACE activity [19]. Of all the fatty acids tested, EPA was the most effective (EPA>ALA>DHA>GLA>LA>AA), whereas AA was the least effective when their ability to inhibit purified ACE activity was tested. DHA and EPA were the most effective fatty acids in inhibiting the leukocyte ACE activity (EPA>DHA>ALA=AA>LA>GLA). On the other hand, PGs (PGE_1, PGE_2, PGI_2, and $PGF_{2\alpha}$) and free radicals (superoxide anion, hydrogen peroxide, and hydroxyl radical) showed marginal (~20%) inhibitory action on ACE activity. In contrast, NO showed powerful inhibitory action on ACE activity [19], whereas PUFAs enhanced eNO generation [20]. The effects of PUFAs on ACE activity and NO generation, and the inability of free radicals and PGs to suppress ACE activity, are interesting because there is a close interaction between platelets, leukocytes, and endothelial cells in the pathogenesis of CHD [8•]. Pro-atherosclerotic events such as hemodynamic forces, hyperlipidemia, hypertension, and smoking induce the expression of proinflammatory genes that initiate and accelerate atherosclerosis at the points of shear stress. These factors enhanced infiltration of intima by leukocytes and macrophages, induced low-level activation of nuclear factor-κB, elevated the expression of vascular cell adhesion molecule-1, intracellular adhesion molecule-1, IL-1, IL-6, and monocyte chemoattractant protein-1, and increased the production and release of free radicals and uncoupling protein expression in endothelial cells, platelets, and leukocytes in atherosclerosis-susceptible regions [21]. These events can be prevented, and the atherosclerosis process and onset of CHD can be arrested if there is adequate production of PGE_1, PGI_2, PGI_3, LXs, resolvins, protectins, maresins, NO, and anti-inflammatory cytokines IL-4, IL-10, and transforming growth factor-β by endothelial cells. These protective molecules will be produced in adequate amounts provided there are sufficient stores of respective precursors such as PUFAs and L-arginine and their respective enzymes in the endothelial cells [8•]. These results suggest that when tissue concentrations of PUFAs are low, the activity of ACE will be high, resulting in increased formation of angiotensin-II and a simultaneous decrease in eNO.

AA, EPA, and DHA are converted in the presence of aspirin to epi-LXs, LXs, and resolvins that possess potent anti-inflammatory actions. Epi-LXs enhance the formation of eNO [3, 6, 8•, 9••, 22]. NO blocks the interaction between leukocytes and the vascular endothelium and stimulates the formation of PGI_2, a potent vasodilator and platelet anti-aggregator, from AA [8•, 22]. This suggests that the beneficial actions of aspirin could be attributed not only to its ability to enhance the formation of PGI_2 and suppress the synthesis of thromboxane A_2, but also to the formation of epi-LXs and eNO. Thus, PUFAs regulate renin formation and action, inhibit angiotensin-II formation by its action on ACE activity, enhance eNO formation, and form precursors to beneficial biologically active molecules such as PGE_1 (from DGLA), PGI_2 (from AA), PGI_3 (from EPA), LXs (from AA, EPA, and DHA), resolvins (from AA, EPA, and DHA), protectins (from DHA), maresins (from DHA), and 5,6-, 8,9-, 11,12-, and 14,15-EETs and hydroxyeicosatetraenoic acids (19- and 20-HETEs; from AA), and thus serve as endogenous regulators of vascular tone, platelet aggregation, and blood pressure [8•, 23••, 24••].

PUFAs Function as Endogenous Diuretics

Healthy volunteers administered EPA (3.9 g) and DHA (2.4 g) every day for 6 weeks showed significant increase in renal plasma flow and glomerular filtration rate, decrease in renal vascular resistance, and an increase in excretion of PGE_3, with no change in blood pressure and heart rate [25]. A diet rich in evening primrose oil (a rich source of GLA and LA) and safflower oil decreased proteinuria, glomerular sclerosis, and tubular abnormalities in diabetic rats [26].

Spontaneously hypertensive rats showed lower systolic blood pressure when fed fish oil (EPA and DHA), evening primrose oil (a rich source of GLA), and fish oil plus evening primrose oil, suggesting that a combination of GLA, EPA, and DHA produces optimal beneficial actions with regard to renal indices and blood pressure [27], while fish oil prevented increase in blood pressure induced by high-salt diet in stroke-prone spontaneously hypertensive rats [28]. These results suggest that availability of optimal amounts of GLA and EPA/DHA reduces blood pressure and preserves renal function in diabetic and hypertensive rats. Thus, PUFAs may show actions similar to those

observed with conventional, synthetic diuretics. These beneficial actions of PUFAs can be attributed to the formation of beneficial PGA, PGE_3, PGI_2, PGI_3, LXs, resolvins, protectins, and maresins.

PUFAs Activate the Parasympathetic Nervous System

Autonomic function is an important factor that regulates heart rate, blood pressure, and cardiac rhythm. Vagal acetylcholine (ACh) and adrenergic norepinephrine and epinephrine regulate the autonomic function and thus the variations in heart rate variability (HRV) and baroreflex sensitivity. n-3 fatty acids reduce the risk of sudden death by preventing life-threatening cardiac arrhythmias by significantly increasing HRV [29]. A direct positive correlation was noted between the content of DHA in cell membranes and HRV index, suggesting an anti-arrhythmic effect of n-3 fatty acids [30]. Because increased parasympathetic tone is responsible for increase in ventricular fibrillation threshold and protects against ventricular arrhythmias, it is likely that EPA/DHA supplementation enhances parasympathetic tone. This is supported by the observation that EPA/DHA supplementation increases hippocampal ACh levels, the principal neurotransmitter of parasympathetic nerves [31]. Hence, it is likely that AA/EPA/DHA supplementation increases brain ACh levels [32, 33], leading to an increase in the parasympathetic tone and thus an increase in HRV and protection from ventricular arrhythmias.

Vagus nerve stimulation also inhibits TNF synthesis in the liver, and ACh significantly attenuated the release of proinflammatory cytokines TNF-α, IL-16, IL-1β, and IL-18 [34–37]. Thus, one mechanism by which PUFAs suppress inflammation could be by augmenting the release of ACh and enhancing the parasympathetic tone.

PUFAs Modulate CETP Activity

High-density lipoprotein cholesterol (HDL-C) is an independent risk factor for CHD. Higher plasma HDL-C is associated with a decreased incidence of CHD. Cholesteryl ester transfer protein (CETP) inhibition produces an increase in HDL by an action that increases reverse cholesterol transport that could prevent atherosclerosis and CHD [38].

In HepG2 cells, AA, EPA, and DHA reduced the levels of CETP mRNA by more than 50% of the control levels, with a corresponding significant decrease in the CETP mass [39], and a significant negative correlation was noted between plasma CETP activity and n-3 fatty acids, suggesting that PUFAs suppress CETP activity [40].

Thus, PUFAs, especially n-3 EPA and DHA, inhibit CETP and HMG-CoA reductase enzyme, and lower plasma triglycerides, cholesterol, and low-density lipoprotein cholesterol with little or no change in HDL-C, but were reported to be effective in arresting atherosclerosis and preventing CHD [41]. These results suggest that EPA and DHA are of use in the prevention and treatment of CHD, and at least a part of these beneficial actions could be attributed to increased formation of LXs, protectins, resolvins, maresins, and nitrolipids.

EPA and DHA Function as Endogenous Anti-Arrhythmic Molecules

PUFAs increased the electrical threshold for the induction of ventricular fibrillation that reduces the risk of developing malignant cardiac arrhythmias [42••]. Mitochondrial dysfunction induced by EFA deficiency could be ameliorated by the presence of normal levels of the EFAs in the n-3—enriched mitochondrial membrane phospholipids [43] that may account for the ability of EPA/DHA to decrease cardiac arrhythmias during myocardial ischemia. The recovery of mitochondrial energy metabolism and myocardial pump function during reperfusion is significantly reduced in n-3 PUFA-enriched hearts, suggesting that EPA and DHA limit myocardial injury during ischemia and reperfusion [42••, 43]. Some of these beneficial actions could be attributed to the formation of LXs, resolvins, protectins, and maresins from various PUFAs [42••].

PUFAs Modulate Telomere and Telomerase Activity

The loss of telomere results in cellular senescence because the cell can no longer divide and replicate itself. Overexpression of telomerase reverse transcriptase (TERT) prevents telomere attrition and enables cells to proliferate indefinitely, a characteristic of cancer cells. Telomere and telomerase are central to aging and several diseases, such as cancer, atherosclerosis, CHD, type 2 diabetes, and hypertension, and to the biology of stem cells.

Telomere shortening has been reported in patients with type 2 diabetes mellitus, hypertension, and insulin resistance [44–48], which are low-grade systemic inflammatory conditions in which plasma levels of various PUFAs are low. NO activates telomerase and delays endothelial cell senescence [49]. Leukocyte telomere length is a predictor of future CHD in middle-aged, high-risk men, whereas pravastatin, an HMG-CoA reductase inhibitor, substantially abrogated shortening of the telomere length in high-risk subjects [50].

n-3 PUFAs are of benefit in type 2 diabetes, hypertension, and hypertriglyceridemia and prevent CHD, in part,

by enhancing NO generation from endothelial cells and decreasing insulin resistance [51•]. Tumor cells undergo apoptosis on exposure to n-3 PUFAs (especially in response to EPA, DHA, and GLA) due to increase in intracellular free radical generation and formation of lipid peroxides [52, 53]. Because NO and lipid peroxides modify telomerase activity, it is likely that PUFAs enhance or decrease activity of TERT in endothelial cells and tumor cells, respectively. This is supported by the observation that EPA and DHA inhibit hTERT activity in human colorectal adenocarcinoma cells [54, 55]. Thus, PUFAs can prevent, reverse, or arrest atherosclerosis and CHD by their ability to enhance eNO synthesis and possibly that of LXs, resolvins, protectins, maresins, and nitrolipids that, in turn, augment hTERT activity and prevent endothelial senescence.

Conclusions

PUFAs, especially EPA, DHA, and possibly GLA, DGLA, and AA, possess aspirin-like action; inhibit HMG-CoA and ACE enzymes; possess diuretic, anti-hypertensive, β-blocker—like actions; and modulate CETP and telomerase activities. PUFAs, especially n-3 fatty acids, enhance ACh levels and increase HRV due to their ability to augment parasympathetic tone. Furthermore, several studies suggested that PUFAs, especially n-3 fatty acids, are useful in the prevention and treatment of Alzheimer's disease, schizophrenia, and depression [7••]. It is important to note that for their optimal action(s) PUFAs need many co-factors, such as folic acid, vitamin B_{12}, vitamin B_6, vitamin C, tetrahydrobiopterin (H_4B), zinc, magnesium, calcium, L-arginine, and small amounts of selenium and vitamin E [4, 11]. Hence, it is important that these co-factors should also be provided in adequate amounts to bring about the beneficial actions of n-6 and n-3 PUFAs. Because statins, glitazones, and many antihypertensive and anti-arrhythmic drugs bring about their actions by modulating EFA/PUFA metabolism, it is likely that subclinical deficiency or altered metabolism of EFAs may subvert their actions/benefits. Some, if not all, of the beneficial actions of PUFAs could be attributed to their products' LXs, resolvins, protectins, maresins, and nitrolipids, and their ability to enhance eNO formation that possess potent anti-inflammatory actions. CHD is a low-grade systemic inflammatory condition, whereas n-3 fatty acids and AA give rise to anti-inflammatory compounds such as LXs, resolvins, protectins, maresins, and nitrolipids. Hence, it is more than likely that the formation of LXs, resolvins, protectins, maresins, and nitrolipids from various PUFAs in the target tissues/cells is responsible for the beneficial actions observed (Fig. 2).

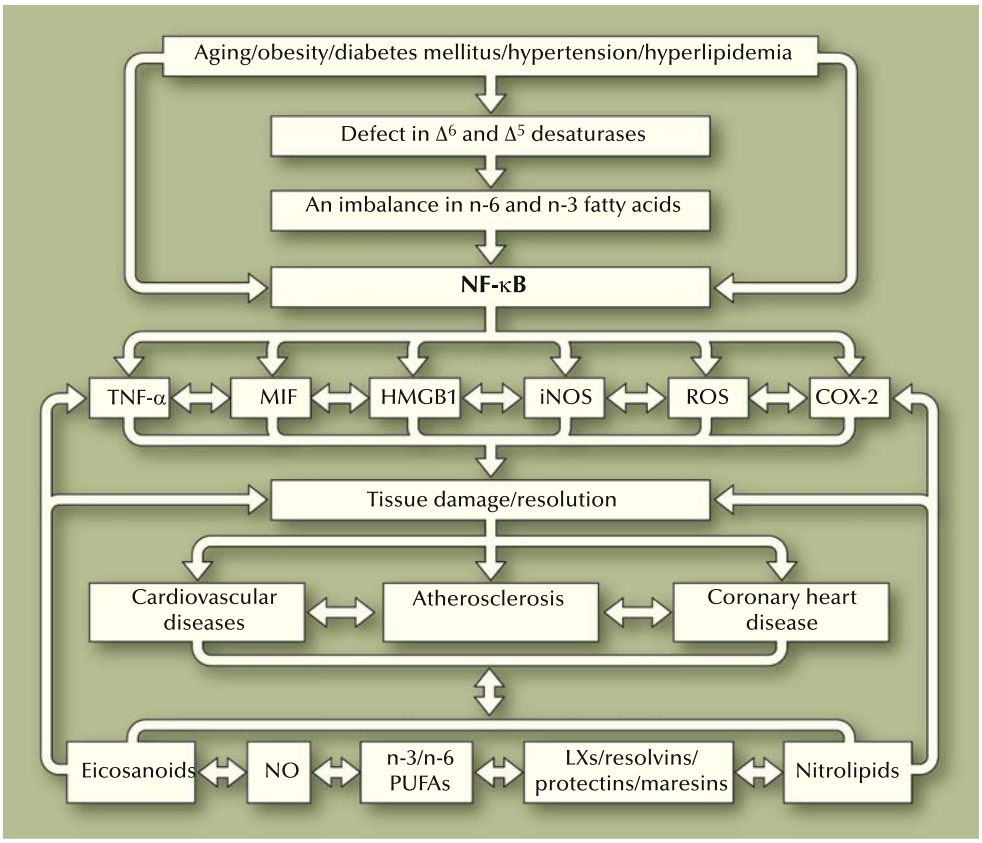

Fig. 2 Schematic showing the relationship between polyunsaturated fatty acids (PUFAs) and cardiovascular diseases. COX-2—cyclooxygenase-2; HMGB1—high-mobility group box 1; iNOS—inducible nitric oxide synthase; LX—lipoxin; MIF—macrophage migration inhibitory factor; n—omega; NF—nuclear factor; ROS—reactive oxygen species; TNF—tumor necrosis factor

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