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Omega-3 polyunsaturated fatty acids and cardiovascular health: a molecular view into structure and function

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ABSTRACT

Given the notorious impact of cardiovascular disease (CVD) as the current leading cause of mortality worldwide, the prevention, identification and management of CV risk factors represents a priority in daily clinical practice. Several studies have shown the beneficial effects of dietary omega-3 polyunsaturated fatty acids (PUFAs) on CV health. Their derivatives, eicosapentaenoic acid and docosahexaenoic acid, intervene in multiple metabolic pathways, including: regulation of the inflammatory response, by reducing the synthesis of pro-inflammatory cytokines; regulation of platelet aggregation, activation and adhesion, by modulating thromboxane A2 and plasminogen activator inhibitor-1 activity; regulation of the coagulation pathways, by reducing the carboxylation of vitamin K-dependent coagulation factors; improvement of endothelial function, given their effects on prostaglandin synthesis and endothelial nitric oxide synthase; reduction of serum lipids, through their effects on the hepatic synthesis of triacylglycerides, beta-oxidation of fatty acids and lipoprotein catabolism; and improvement of myocardial function via their membrane-stabilizing effects, and an increase in fluidity, size and distribution of membrane lipid rafts. Nevertheless, these effects appear to vary according to the type of PUFA ingested, dietary sources, daily dosing and individual factors inherent to the subject. Therefore, further studies are required to determine the ideal supplementation for each kind of patient and their particular CV profiles.

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INTRODUCTION

Cardiovascular disease (CVD) represents an ongoing global epidemic. In 2014, 27.6 million people were diagnosed with CVD worldwide,[1] and by 2030, it may be responsible for up to 23.5 million deaths yearly.[2] These trends are common in all westernized countries, including Latin America. In Venezuela, 29.47% of all mortality was attributed to CVD in 2012.[3] Given the heavy burden CVD represents for public health systems, prevention has become a key component in clinical practice and research, oriented to the identification and management of several risk factors, both modifiable and non-modifiable.[4] Regarding modifiable risk factors, westernized dietary patterns, notable for their high intake of dairy products, refined carbohydrates and saturated fats, have been strongly linked with the development of not only CVD, but also hypertension (HTN), obesity and type 2 diabetes mellitus.[5-7]

In 1980, Bang *et al*.[8] studied the diet of the Eskimo population of Greenland, characterized by high intake of foods rich in long chain polyunsaturated fatty acids (LC-PUFAs), and paradoxically found a low incidence of CVD in these individuals.[9] From these pioneer studies, different epidemiological and interventional investigations have backed the cardioprotective role of n-3 LC-PUFAs.[10,11]

Although many beneficial CV effects have been ascribed to PUFAs, including hypolipidemic, antithrombotic, antihypertensive and antiarrhythmic properties,[12,13] the underlying molecular mechanisms remain to be elucidated. This review aims to offer an integrated state-of-the-art vision into the structure of PUFAs and their functions in the CV system.

GENERAL OVERVIEW OF PUFAS

Structure and classification

Fatty acids are molecules consisting of a long linear hydrocarbon chain that generally contains a pair number of carbon atoms between 12 and 24, with a carboxyl (-COOH) group in one end and a methyl (-CH3) group in the other.[14] They are termed saturated fatty acids when only simple bonds exist between the carbon atoms, while those that have one or more double bonds are known as unsaturated fatty acids.[15] The latter include widely recognized nutritionally essential molecules for humans and other animal species, including linoleic acid (LA) and α-linoleic acid (ALA).[16]

Fatty acids with more than one double bond in their chain are called PUFAs, which are classified in 2 main subgroups: n-6 long chain PUFAs (n-6 LC-PUFAs) and n-3 long chain PUFAs (n-3 LC-PUFAs), which are commonly referred to as omega-6 and omega-3 PUFAs, respectively.[17] The former are LA derivatives with 2 double bonds, which are located 6 carbons away from the methyl end (18:2Ω6); whereas n-3 LC-PUFAs derive from ALA and have 3 double bonds, with the first one being in the third carbon of the chain (18:3Ω3)[18,19] [Figure 1].

Metabolism and general biologic functions of essential PUFAs

The metabolism of both types of PUFAs ends in the formation of eicosanoids, which are biologically active compounds including prostaglandins (PGs), thromboxanes (TXs) and leukotrienes (LTs).[18] As shown in Figure 1, arachidonic acid (AA) is synthetized from LA (n-6), and is converted by the action of cyclooxygenase (COX) and lipoxygenase (LOX) into 2-series PGs and TXs and 4-series LTs and lipoxines. Although these mediators intervene in both the establishment and resolution of the inflammatory response, their net effect is predominantly pro-inflammatory.[19,20] In contrast, ALA (n-3) is a precursor of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), from which 3-series PGs and TXs, as well as 5-series LTs, lipoxins, resolvins and neuroprotectins are derived. These compounds have chiefly anti-inflammatory effects,[17] which is why current nutritional guidelines are oriented towards an increase in n-3 PUFAs intake.[21-24] Furthermore, the products of both series mediate the regulation of other physiological processes, such as the maintenance of cell membrane architecture, especially through their arrangement in lipid rafts,[25,26] and play a role in hemostasis and vasoconstriction, which are further explained ahead.[18,27]

Role of PUFAs in cell membrane maintenance

The long hydrocarbon chains and double bonds in EPA and DHA exert modifications on the cell membrane due to their length and degree of unsaturation.[28] These molecules have been demonstrated to increase membrane fluidity and modify the size and distribution of lipid rafts in aortic endothelial cells and rat lymphocyte cultures.[29,30] Lipid rafts are dynamic membrane microdomains containing sterols, enriched sphingolipids and specific binding proteins, which attain a metastable resting state through a constellation of lipid-lipid, protein-lipid and protein-protein bonds.[31] Incorporation of n-3 PUFAs in lipid rafts results in decreased cholesterol and sphingolipids in these microdomains.[32] This has been confirmed by systematic studies in membrane models that suggest

cholesterol to be incompatible with environments rich in highly unsaturated lipids, as observed in phospholipid bilayers containing DHA.[33]

Most of the research on n-3 PUFAs in membrane models has centered around DHA.[34] This molecule is deemed unique because it contains six double bonds and is very flexible, with quick rearrangements amidst multiple conformational states.[29] Spectrometry studies have revealed DHA-containing phospholipids to form their own domains with a different arrangement in presence of sphingolipids and cholesterol, excluding saturated acyl chains from their structure.[35] In addition, because n-3 PUFAs tend to reject cholesterol, DHA-containing phospholipids tend to create non-raft domains which may be physically separated on cell membranes. This allows proteins to more readily occupy a space according to its requirements in a specific domain or in amplified rafts.[36] An alternative model points out that n-3 PUFAs are probably incorporated in the rafts as nanodomains, forcing cholesterol out of rafts.[26] This model is also applicable to proteins within lipid rafts, where incorporation of n-3 PUFAs into lipid rafts forces proteins to relocate to non-raft domains.[26] Further research is required to fully understand the biologic importance and mechanisms underlying the lateral organization of lipid microdomains in cell membranes, as well as the modulatory effects of n-3 PUFAs in this context.[32]

MOLECULAR MECHANISMS OF PUFAS IN CARDIOVASCULAR HEALTH

Chronic pro-inflammatory states

The anti-inflammatory effects of n-3 PUFAs have been widely reported.[37-40] One of the central mechanisms is the down-regulation of the synthesis of pro-inflammatory cytokines such as tumor necrosis factor alpha, interleukin 6 and monocyte chemoattractant protein-1 (MCP-1)[41-44] in adipose tissue. This occurs when EPA and DHA bind to the G-protein coupled receptor (GPR120) in macrophages and adipocytes, causing its activation and internalization with β-arrestin-2, and forming the GPR120/β-arrestine-2 complex.[45] This complex is then dissociated into the transforming growth factor beta (TGF-β) activated kinase 1 binding protein 1 (TAB1) that results in the inhibition of TGF-β activated kinase 1 (TAK1), and thus the down-regulation of the nuclear factor kappa B (NF-κB) and the inhibition of its function.[44] Besides, the incorporation of DHA to the lipid membrane disrupts the signaling of toll-like receptor 4 (TLR-4) by impeding its translocation to the lipid raft, and inhibiting the signaling pathway of MD2/TRIAP-MyD88/IRAK-TRAF6/IKKβ[41,46,47] [Figure 2]. Also, EPA and DHA cause the down-regulation of nicotinamide adenine dinucleotide phosphateoxidase, which induces the production of reactive oxygen species, a requirement for TLR-4 signaling.[41,42] These pathways converge in the inhibition of NF-κB, diminishing the inflammatory

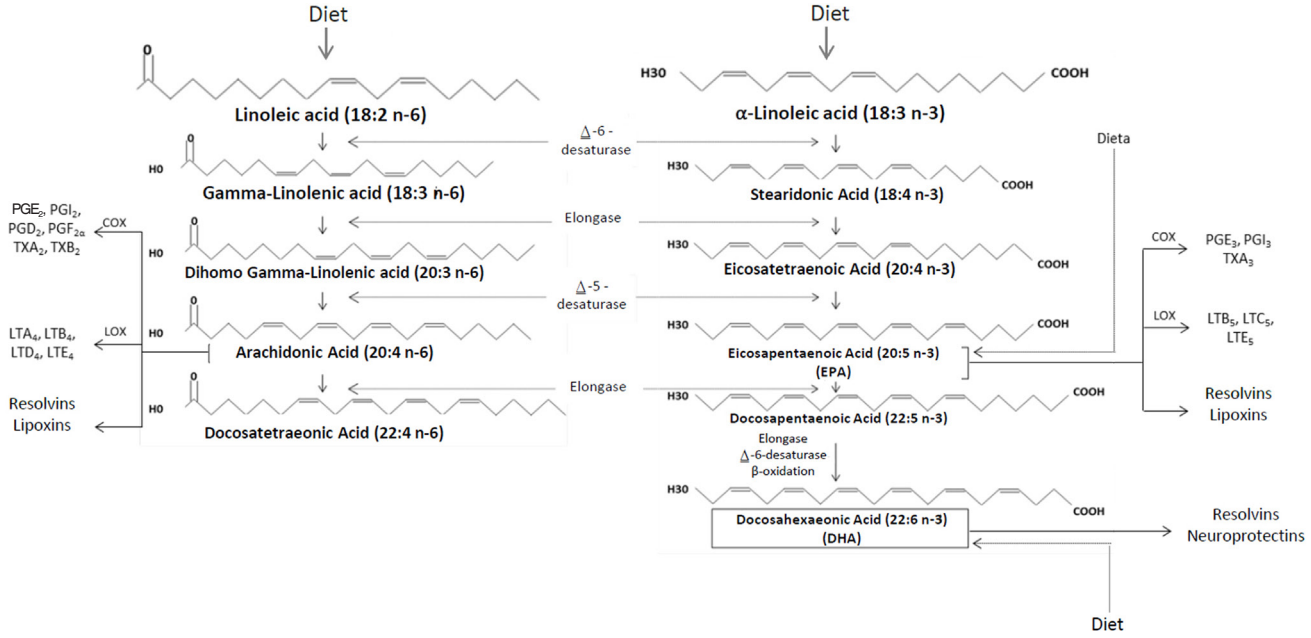

Figure 1: Metabolism of n-6 and n-3 polyunsaturated fatty acids. n-3 and n-6 polyunsaturated fatty acids are derived from linoleic acid (LA) and α-linoleic acid (ALA). Through various enzymatic reactions, LA is converted into arachidonic acid, responsible of the formation of mainly proinflammatory PG and TX. On the other hand, ALA is converted into EPA and DHA, which derive into mostly antiinflammatory PG and TX. PGE2: prostaglandin E2; PGD2: prostaglandin D2; PGF2α: prostaglandin F2α; PGI2: prostacyclin I2; PGE3: prostaglandin E3; PGI3: prostacyclin I3; TX: thromboxanes; LT: leukotrienes

response.[44,45] In addition n-3 PUFAs may also prevent macrophage infiltration in adipose tissue.[41]

Thrombogenesis

The antithrombotic properties of PUFAs have been described since the 1980s, owing to the pioneer studies by Bang and Dyerberg.[48] These studies demonstrated that the Eskimo diet, characterized by high intake of seafood rich in n-3 PUFAs (mainly fish, seal and whale), was associated with a low incidence of CVD, as well as a decrease in thrombogenesis, evident by high incidence of hemorrhages.[49,50]

Even though these effects have been described in populations of different latitudes,[51-53] the inverse relation between n-3 PUFAs intake, platelet aggregation, coagulation and fibrinolysis is still not completely elucidated;[54] however, both *in vitro* and *in vivo* studies have reported that n-3 PUFAs supplementation reduces TXA2 synthesis, platelet activation and adhesion,[55] and decreases plasminogen activator inhibitor-1 (PAI-1) activity and concentration.[56]

The mechanisms by which n-3 PUFAs decrease thrombogenesis have been extensively studied, especially in platelets. High n-3 PUFA intake, especially EPA and DHA, appears to favor the replacement of AA in cell membrane phospholipids, decreasing the binding rate of AA to COX-1, resulting in reduced TXA2 synthesis, a vasoconstriction and platelet aggregation-promoting molecule.[57] On the other hand, this secondarily increases the production of TXA3, which exerts a significantly lower biological activity than TXA2.[58] Another mechanism observed with *in vivo* studies is the capacity of n-3 PUFAs to act as TXA2 and PG H2 antagonists, through the synthesis of protectin DX, a product of DHA dihydroxylation obtained by the action of LOX.[59] This compound also has the capacity to inhibit both COX-1 and COX-2 in platelets and neutrophils, significantly decreasing both platelet activation and aggregation [Figure 3].[60,61]

In contrast, views on the mechanisms underlying the anticoagulant effects of n-3 PUFAs remain controversial. Some studies suggest these molecules may interfere in the carboxylation of vitamin K-dependent coagulation factors II, VII, IX and X;[62,63] while other studies attribute more relevance to a modification in serum fibrinogen levels.[64] Similarly, the role of n-3 PUFAs in fibrinolysis remains unclear,[65] however it has been proposed that by unknown mechanisms, they alter PAI-1 synthesis through a genetic pathway.[66]

Dyslipidemia

The effects of n-3 PUFAs on serum lipids were also first ascertained by Bang and Dyerberg[67] in their emblematic study on the Eskimo population. Results of this study showed that individuals who stayed in their birthplace had lower levels of triacylglycerides (TAG), very low-density lipoproteins (VLDL-C) and low-density lipoproteins (LDL-C), whereas those who later migrated to Denmark showed a serum lipid profile similar to

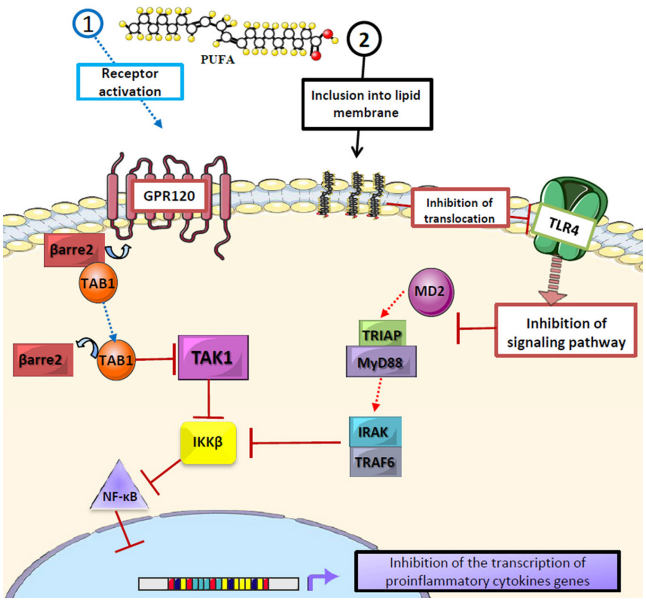

Figure 2: Role of polyunsaturated fatty acids in proinflammatory cytokine synthesis. EPA and DHA inhibit the production of proinflammatory cytokines through different mechanisms: (1) binding of EPA and DHA to the G protein-coupled receptor (GPR120) leads to its activation and binding to β arrestin-2, which then dissociates into TAB1 and inhibits TAK1, thus interrupting the IKKβ/NF-κB cascade; (2) the inclusion of EPA and DHA into the lipid bilayer, which modifies lipid rafts and interrupts the translocation of TLR-4 and the MD2/TRIAP-MyD88/IRAK-TRAF6/IKKβ/NF-κB pathway, thus inhibiting the production of cytokines, showing the antiinflammatory action of EPA and DHA

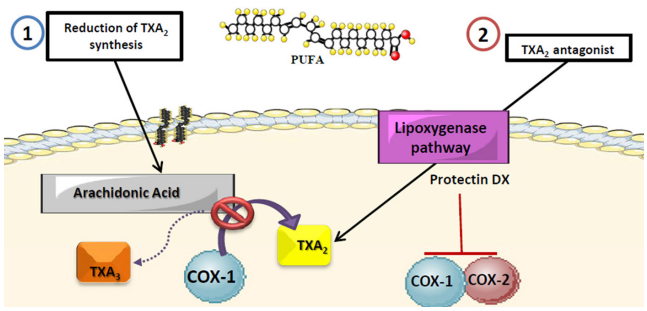

Figure 3: Role of polyunsaturated fatty acids in thrombogenesis. n-3 PUFAs exert their antithrombotic effect on platelets via two main processes: (1) replacement of arachidonic acid in the platelet membrane, which causes a decrease in the action of COX-1 on arachidonic acid, diminishing TXA2 synthesis and favoring the synthesis of TXA3; (2) activity as TXA2 antagonists through the synthesis of protectin DX, a molecule from the lipoxygenase pathway, which inhibitis COX-1 and COX-2. PUFA: polyunsaturated fatty acids; TXA2: thromboxane A2; TXA3: thromboxane A3; COX-1: cyclooxygenase 1; COX-2: cyclooxygenase 2

that of the Danish population. Thus, environmental factors - namely dietary n-3 PUFA intake - may exert a preponderant impact on serum lipids.[68]

Among these actions on lipid metabolism, the TAG-lowering effect has been found to be the most robust in large epidemiological studies;[69] however, it appears to be largely modifiable by the overall dietary composition, as elevated carbohydrate and saturated fat intake may surpass the effect of n-3 PUFAs due to increased TAG synthesis and storage.[69,70] In addition, the magnitude of the lipid-lowering effect of n-3 PUFAs depends on each subject's basal serum lipid levels, as greater decreases are observed in subjects with higher TAG levels.[70,71]

The mechanisms by which n-3 PUFAs achieve these effects on TAG are related to the decrease of their hepatic synthesis via competitive inhibition of the enzymes involved, especially 1,2 diglyceride acyltransferase, which catalyzes the conversion of diacylglycerides into TAG.[72] In addition, PUFAs have high affinity for several peroxisome proliferator-activated receptor (PPAR) subtypes, particularly PPAR-α, a nuclear transcription factor highly expressed in adipose tissue and skeletal muscle.[73] When PPAR-α is activated by specific substrates like PUFAs, it favors the synthesis of enzymes involved in lipid catabolism.[74] Therefore, n-3 PUFA intake promotes the β-oxidation of fatty acids in peripheral tissues, which contributes to the catabolism of circulating TAG in chylomicrons and VLDL-C. This results in diminished traffic of non-esterified fatty acids to hepatocytes, causing an additional reduction in the input of substrates for TAG synthesis, further decreasing the hepatic production of VLDL-C.[72]

Additionally, PUFAs downregulate the sterol regulatory element-binding protein 1c (SREBP1c), which modulates the expression of genes involved in the synthesis of fatty acids and TAG.[75,76] PUFAs inhibit SREBP1c activity in the liver by antagonizing the liver X receptor alpha, a nuclear receptor found in hepatocytes that regulates the synthesis of SREBP and the SREBP inhibitor protein.[77,78] Another reported genetic mechanism is the ability of PUFAs to inhibit the hepatic maturation of the carbohydrate-responsive element-binding protein, a transcription factor related to the expression of enzymes involved in TAG synthesis[79] [Figure 4].

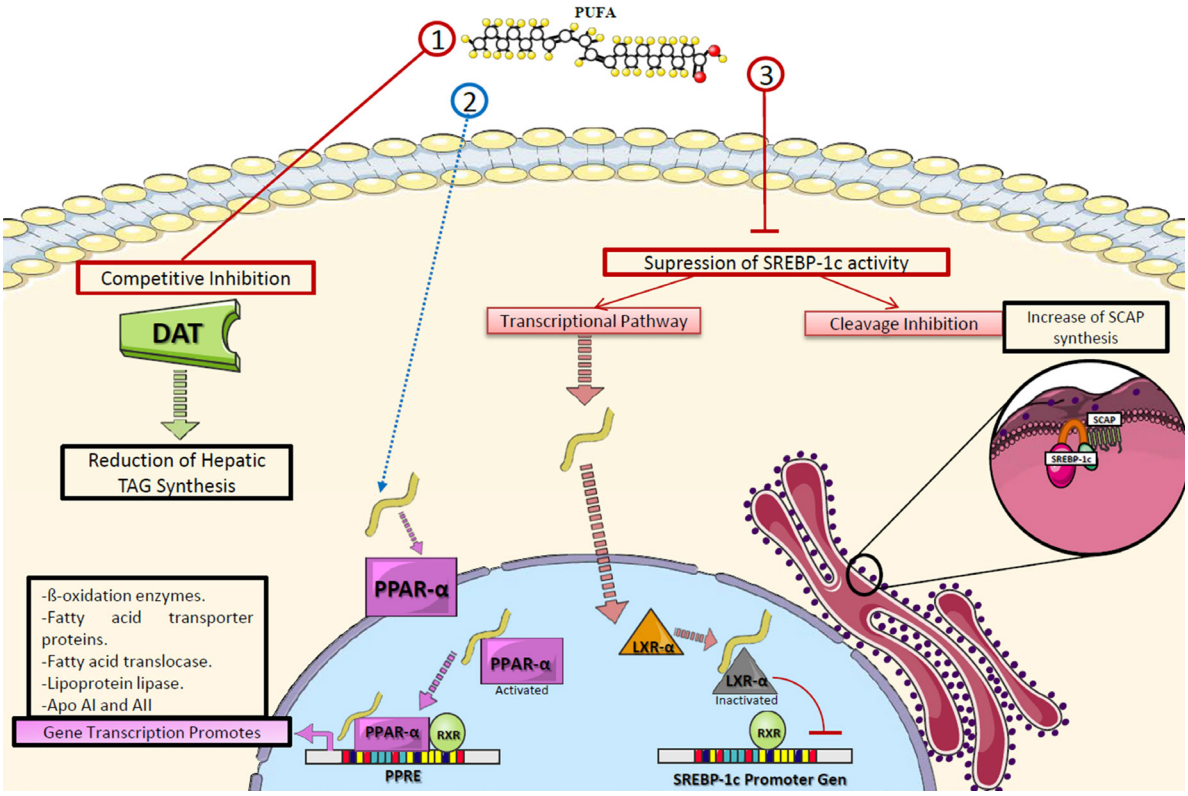

Figure 4: Role of polyunsaturated fatty acids in triacylglyceride metabolism. PUFAs decrease TAG through various mechanisms: (1) competitive inhibition of DAT; (2) activating PPAR-α, which promotes the transcription of enzymes involved in lipolysis and fatty acid transport; (3) suppressing the activity of SREBP-1c which regulates the expression of genes involved in fatty acid and TAG synthesis. PUFA: polyunsaturated fatty acid; DAT: 1,2 diglyceride acyltransferase; TAG: triacylglycerides; PPAR-α: peroxisome-proliferator activated receptor alpha; RXR: retinoid X receptor; LXR-α: liver X receptor alpha; SREBP-1c: sterol regulatory element-binding protein 1c; SCAP: SREBP inhibitor protein; PPRE: PPAR response elements

These TAG-lowering mechanisms are accompanied by a secondary decrease of VLDL-C: *in vitro* studies have described PUFA-mediated activation of non-proteosomal degradation of apolipoprotein B (Apo B). This protein, found in the membrane of chylomicrons, LDL-C and VLDL-C, allows the transport of lipids towards peripheral tissues.[80] Activation of this pathway results in the selective degradation of the Apo B which would have been integrated into naïve VLDL, thus reducing liver secretion of this lipoprotein.[81,82]

Several randomized studies have shown that PUFAs also contribute to a slight increase of high density lipoprotein (HDL-C), ranging between 2.3-7.9% for EPA, and 2.9-18.3% for DHA.[83,84] PUFA-mediated reduction of cholesteryl ester transfer protein (CETP) activity may be accountable for this effect, as it would lead to a decrease in the net flow of cholesterol esters from HDL-C to LDL-C and VLDL-C. Recent *in vitro* studies also suggest PUFAs to be regulators of CETP and apolipoprotein A1 gene expression.[85,86]

On the other hand, the effects that PUFAs exert on LDL-C are yet to be defined. A study on adult women by Ooi *et al*.[87] where the effects of diets with high and low fish intake (1.23 g/day and 0.27 g/day of EPA and DHA, respectively) were assessed showed a non-significant decrease in serum LDL-C levels for both diets. However, significantly lower Apo-B100 concentration, greater LDL-C Apo-B100 production rate and higher conversion percentage of TAG-rich lipoproteins (TRL) into LDL-C were reported in high fish intake diets. Other studies have reported that EPA and DHA supplement intake considerably increases LDL-C levels when compared to placebo and EPA-exclusive intake.[88] However, recent evidence suggest that EPA as opposed to DHA has more prominent effects on LDL in patients with hyper-TG due to its antioxidant properties in various Apo B-containing proteins,[89] improving secondarily endothelial function and inflammatory profile.[90] Studies in animals suggest that very high intake of PUFAs of marine origin increases the union of the TRL to the endothelial LPL, prolonging the interaction period and thus resulting in a boost of LDL-C formation. Furthermore, very high intake of n-3 PUFAs has been found to boost the production of smaller TRL with less amount of Apo-E, which show a tendency to convert into LDL-C;[91] as well as increase the expression of hepatic LDL-C receptors, amplifying its catabolism.[92] Indeed, the effects of PUFAs on LDL-C levels appear to significantly vary across specific PUFA types and quantity.[88,89]

Hypertension

The role of HTN as one of the main independent risk factors for CVD has been widely recognized along with the role of n-3 PUFAs on its management.[7] However, recent findings have shown that maintaining normal blood pressure (BP) levels even in non-hypertensive individuals significantly lowers the incidence of CVD, representing important evidence for the use of n-3 PUFAs as a powerful preventive intervention.[93] A recent study by Huang *et al*.[94] on 1,154 Chinese adults found hypertensive subjects to have lower plasma PUFA concentrations when compared to healthy counterparts. This echoes the results of a previous study on 447 Eskimo people, where both high dietary intake and elevated plasma levels of n-3 PUFAs were associated with lower levels of diastolic blood pressure.[95]

PUFAs may regulate BP through various mechanisms, most powerfully through conversion into vasodilator PG and promotion of renin release from the kidney.[96] Moreover, it has been demonstrated that a diet rich in n3-PUFAs suppresses the activity of the angiotensin-converting enzyme, reduces the formation of angiotensin II, improves the generation of eNO (endothelial nitric oxide) and suppresses the expression of TGF-β.[97] Recently, in murine models with angiotensin II-dependent HTN, the combination of a soluble epoxide hydrolase inhibitor along with a diet rich in n3-PUFAs was tested, showing higher levels of EPA and DHA epoxides and a reduction of inflammatory markers in the kidney (PGs and MCP-1), contributing to a decrease in systolic BP and inflammation.[98]

Various cytochrome P450 (CYP) isoforms have also been identified in the physiological production of active metabolites of AA, EPA and DHA as alternative substrates.[99] In this context, Agbor *et al*.[100] demonstrated the contribution of isoform CYP1A1 tothe metabolism of n3-PUFAs, and the activation of endothelial nitric oxide synthase and consequent increase innitric oxide (NO) bioavailability associated with a diet rich in n3-PUFAs [Figure 5].

Furthermore, a study by Hoshi *et al*.[101] exposed the activation of large conductance Ca^{2+}-activated K^+ channels by DHA, through a fast and reversible stimulus independent of Ca^{2+} concentration. However, the exact bonding site remains to be identified. The activation of these channels in smooth muscle cells allows passive K^+ efflux, which translates into the hyperpolarization of the cell membrane and thus its hypotensive effect.[102]

On the other hand, modifications in fatty acid composition in the lipid matrix of the cell membrane play an important role in the pathogenesis of hypertension.[103] A decrease of PUFAs in the cell

membrane of erythrocytes leads to a decrease in the negative charge of the membrane, with reduced phospholipid fluidity, activation of the synthesis of proinflammatory eicosanoids, and increased sensitivity of arterial smooth muscle cells to vasoconstrictive effects.[103,104]

Myocardial function

Reports from different human and animal models have demonstrated that n-3 PUFAs improve left ventricular inotropic function, without causing hypertrophy or increase in blood pressure.[105] The underlying mechanism involves an increase in the activity of myosin ATPase and Na^+/K^+ ATPase, and the expression of Ca^{2+} ATPase in the sarcoplasmic reticulum, which are associated with positive inotropism, and maintenance of intra-sarcoplasmic reticulum calcium concentration and the sodium calcium exchanger (NCX).[106,107] Furthermore, an indirect effect is achieved through an increase in ventricular efficiency, which is defined as the production of the highest ejection volume with the lowest possible oxygen consumption, and the decrease in blood pressure.[108] This is possible due to the incorporation of DHA in the cell membrane,[109] influencing the eicosanoids mechanism and modulating cellular Ca^{2+} and its signaling pathways.[110] On the other hand, it has also been attributed to the shortening in the monophasic action potential due to the suppression of ATP-dependent K^+ channels in the sarcolemma.[111]

Another proposed mechanism is the increase in the Na^+/K^+ ATPase activity, which boosts Na^+ concentrations, diminishing the intracellular Ca^{2+} concentrations due to its effect in NCX activity in the cell membrane.[112] In addition, it has been demonstrated that the Na^+/K^+ ATPase activation modulates the function of L-type Ca^{2+} channels, which causes a greater release of calcium by the sarcoplasmic reticulum and higher intracellular Ca^{2+} gradients during systole, increasing contraction strength.[113]

Cardiac arrhythmia

Several studies have reported an association between n-3 PUFA intake and a lower risk of CVD-related death, specifically from ischemic events, where the myocardium is more prone to suffer irregularities in its electric activity that can lead to sudden death.[114,115]

Myocardial cells at the border of the ischemic zone have a relatively depolarized resting potential and can potentially generate ventricular fibrillation because of how easily they can be excited.[114] Because of this, an elevation in n-3 PUFAs stabilizes the high excitability of these partially depolarized cells in the ischemic myocardium. This prevents spontaneous or premature depolarization,[116] resulting in a longer refractory period and an increase in the voltage needed for the cellular depolarization.[117-120] More specifically, n-3 PUFAs can inhibit voltage-dependent Na^+, K^+ and Ca^{2+} channels, as well as Na^+/Ca^{2+} exchangers and Ca^{2+}-activated K^+ channels.[121] Consequently, these changes lower membrane excitability,[122] translating to a net membrane-stabilizing effect.[116,123]

Finally, an antiarrhythmic mechanism has been implicated in the role that n-3 PUFAs play in autonomic control, by increasing the vagal tone.[124,125] Recent

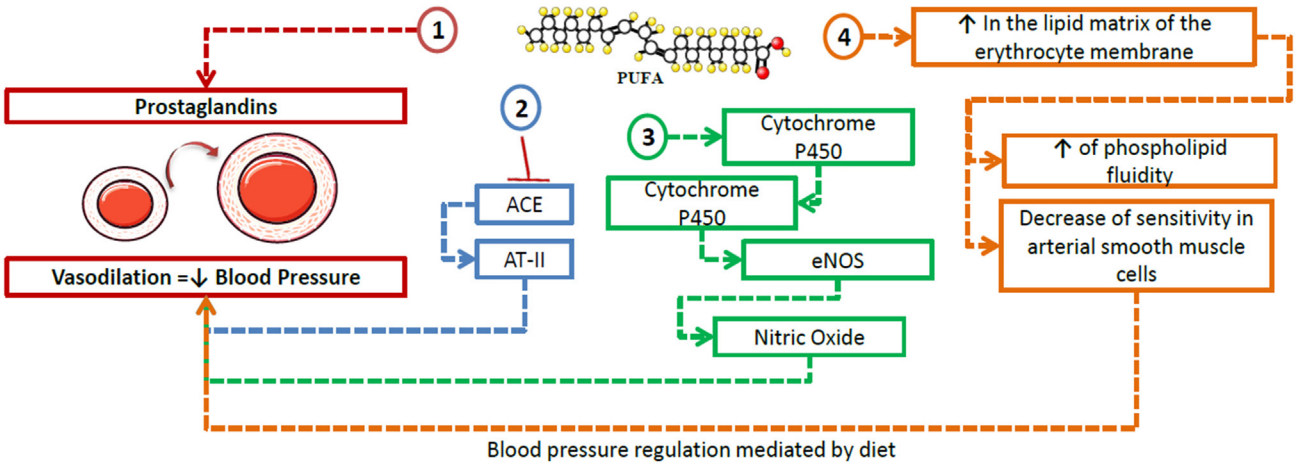

Figure 5: Role of polyunsaturated fatty acids in hypertension. n3-PUFAs intervene in blood regulation through the following pathways: (1) conversion into prostaglandins via the cyclooxygenase pathway, causing vasodilation of the smooth muscle in arterial walls; (2) inhibition of ACE, reducing the synthesis of AT-II, thus leading to a decrease in blood pressure; (3) promotion of cytochrome P450 isoforms such as CYP1A1, which contributes to the activation of eNOS, increasing the bioavailability of nitric oxide and thus causing vasodilation; (4) incorporation into the lipid matrix of the erythrocyte membrane, where they lead to a an increase, and a decrease in the sensitivity of arterial smooth muscle cells to vasoconstrictive effects. ACE: angiotensin-converting enzyme; AT-II: angiotensin II; eNOS: endothelial nitric oxide synthase; PUFA: polyunsaturated fatty acids

evidence highlights that the effect n-3 PUFAs exert on the electrophysiology of the ventricles and atria relies on their favorable action on cell-cell connections by modulating the expression and phosphorylation of connexin-43[125,126] [Figure 6].

Ischemia/reperfusion

Although the restoration of blood flow in the ischemic myocardium is essential for tissue survival during acute myocardial infarction, its reperfusion may directly accelerate the ischemic process or increase the myocardial injury in a phenomenon known as "reperfusion injury".[127-129] Important studies have reported that this event is responsible for up to 50% of the final infarction size.[130] PUFAs appear to be associated with reduced ischemic/reperfusion injury and thus with a better recovery after a coronary event.[131]

During ischemia/reperfusion, increased n-3 PUFA content in the mitochondrial membrane may contribute to stabilization and thus lower myocardial oxygen consumption (MVO_2), thereby attenuating the thermodynamic inefficiency caused by hypoxia.[132,133] In addition, a lower MVO_2 could diminish vulnerability to arrhythmia through the energetic maintenance of transmembrane potentials during episodes of ischemia.[133]

A study on 211 patients with ST segment elevation myocardial infarction who underwent reperfusion by percutaneous coronary intervention found patients with higher levels of n-3 PUFAs (EPA + DHA ≥ 155 mg/mL) had a lower incidence of reperfusion injury than those with lower levels of n-3 PUFAs (EPA + DHA < 155 mg/mL).[134] Although the antiarrhythmic effect may exert the most potent impact in ischemia/reperfusion injury,[135] other supplementary actions may also intervene, including antithrombotic, anti-inflammatory and vasoactive effects.[136-138]

CONCLUSION

As has been described in review, n-3 PUFAs boast several beneficial effects in CV physiology and pathophysiology [Figure 7]. Notwithstanding current available evidence supporting the administration of n-3 PUFAs as a therapeutic intervention in CVD, further research is required to better characterize the underlying molecular mechanisms, as well as refine recommendations for their clinical use. Indeed, one

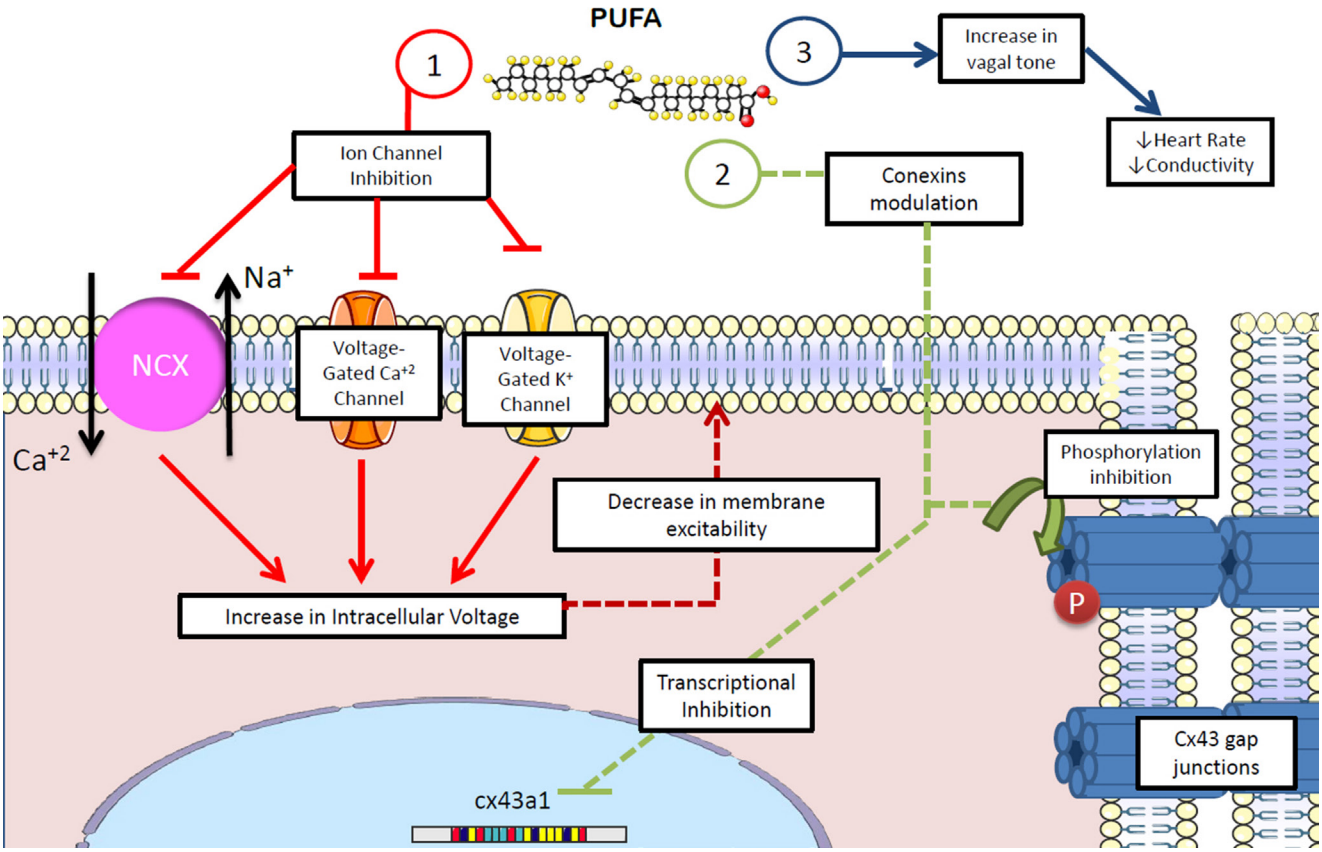

Figure 6: Antiarrhythmic effects of polyunsaturated fatty acids. n-3 PUFAs show several potential antiarrhythmic properties: (1) membrane potential stabilization by decreasing transmembrane io traffic; (2) inhibition of the activity and expression of connexins, decreasing the conductivity of myocardial tissue; (3) increase in vagal tone, decreasing heart rate, conductivity and myocardial excitability. NCX: sodium-calcium exchanger; Cx43: connexin-43; PUFA: polyunsaturated fatty acids

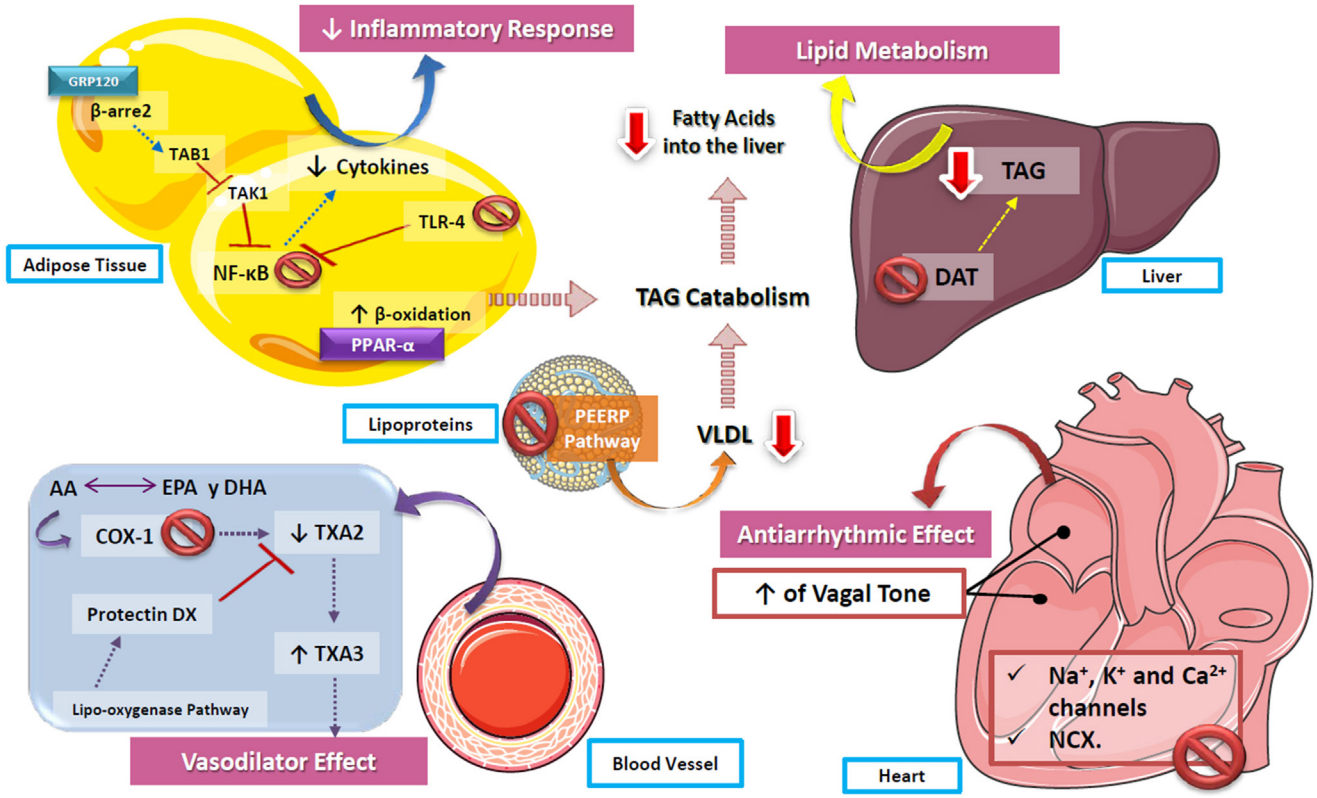

Figure 7: Role of polyunsaturated fatty acids in cardiovascular function. The actions of n3-PUFAs are diverse, including the decrease of the inflammatory response via NF-kB inhibition, as well as an increase of β-oxidation, causing the catabolism of triaclyglycerides and contributing to the decrease of lipids stored both in the liver and vessel walls. In addition, by increasing the production of TXA3 in vessel walls, PUFAs decrease vascular resistance, reducing blood pressure. On the other hand, one of the most described effects of n3-PUFAs is their action on cardiac arrhythmia, by inhibiting voltage-gated ion channels and exchangers, as well as increasing the vagal tone of the atria and ventricles, which leads to a lower heart rate. PUFA: polyunsaturated fatty acids; TXA2: thromboxane A2; TXA3: thromboxane A3; COX-1: cyclooxygenase 1; DAT: 1,2 diglyceride acyltransferase; TAG: triacylglycerides; NF-kB: nuclear factor kappa B; TLR-4: toll-like receptor 4; VLDL: very low-density lipoproteins

of the most pressing issues is the assessment of potential adverse effects linked to the therapeutic implementation of n3-PUFAs, along with the determination of adequate dosing and sources for these molecules in a myriad of specific clinical scenarios.

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There are no conflicts of interest.

Patient consent

Not applicable.

Ethics approval

Not applicable.

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