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Cardioprotective effects of omega 3 fatty acids: origin of the variability

Jérôme Roy¹ · Jean-Yves Le Guennec^{1,2}

Abstract Since 40 years, it is known that omega-3 poly-unsaturated fatty acids (ω 3 PUFAs) have cardioprotective effects. These include antiarrhythmic effects, improvements of autonomic function, endothelial function, platelet anti-aggregation and inflammatory properties, lowering blood pressure, plaque stabilization and reduced atherosclerosis. However, recently, conflicting results regarding the health benefits of ω 3 PUFAs from seafood or ω 3 PUFAs supplements have emerged. The aim of this review is to examine recent literature regarding health aspects of ω 3 PUFAs intake from fish or supplements, and to discuss different arguments/reasons supporting these conflicting findings.

Keywords ω -3 PUFA · Sarcomere proteins · Cardiac arrhythmias · Controversies

Introduction

Fish is a good source of protein and, unlike fatty meat products, it is poor in saturated fat. Fish is also a good source of omega-3 poly-unsaturated fatty acids (ω 3 PUFAs). Forty years ago, the cardiovascular beneficial effects of ω 3 PUFAs were first noticed when researchers identified lower rates of cardiovascular disease among

Greenland Inuit, whose diet consisted of foods rich in ω 3 PUFAs, such as whale, fish and seal, compared to the Danish population (Bang et al. 1976). By comparing plasma and food lipid profiles of both populations, the authors concluded that there was an association between dietary pattern and the incidence of cardiovascular disease. Also, a diet rich in ω 3 PUFAs is associated with lower serum cholesterol and triglycerides, slower atherosclerotic plaque growing rate, and slightly lower arterial blood pressure (De Caterina 2011). Since then, epidemiological, clinical, animal and cellular studies confirmed these beneficial effects (Billman 2013). Consequently, the American Heart Association (AHA) recommends eating at least two serving (particularly oily) fish per week. ω 3 PUFAs have thus generated considerable interest as well as controversies regarding their impact on cardiovascular physiology. A number of observational studies have shown that consumption of fish leads to a reduction of sudden cardiac death incidence (Burr et al. 1989; Siscovick et al. 1995). However, from the end of the 20st century, researchers failed to demonstrate a convincing cardioprotective effect and ignited the debate on whether PUFAs have healthy effects (Salonen et al. 1995; Ascherio et al. 1995; Kromhout et al. 1996; Pietinen et al. 1997; Guallar et al. 1999; Gillum et al. 2000; Oomen et al. 2000; Rissanen et al. 2000; Iso et al. 2006; Wilhelm et al. 2008; Yamagishi et al. 2008). As reviewed by Moreno et al. (2012), ω 3 PUFAs have various effects on cardiac ion currents that could explain the contradictory effects of ω 3 PUFAs. These differences appeared to depend on whether the ω 3 PUFAs were applied to cells or formerly incorporated in membranes modifying its composition and, thus, the effects on cell signalling. In this paper, we review the experimental evidence supporting that the actions of ω 3 PUFAs are due to pleiotropic mechanisms.

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Environmental parameters

ω 3 PUFAs have pleiotropic actions including cardioprotective effects, especially against post-infarction arrhythmias (Saravanan et al. 2010; Schuchardt et al. 2011). Recently, new drugs have been added to the standard treatment of cardiac pathologies, such as statins. The introduction of statins, a drug class used to lower LDL-cholesterol level by inhibiting HMG-COA reductase, can modulate ω 3 PUFAs effects by interfering with their metabolism (de Lorgeril et al. 2013). The mechanism of action is still not well understood, but it seems that mitochondria could be involved, especially coenzyme Q10. In agreement with this hypothesis, a European secondary prevention clinical trial reports that ω 3 supplementation (alpha-linolenic acid, Eicosapentaenoic acid; EPA and docosahexaenoic acid; DHA) reduces the incidence of cardiovascular events by half only when statins were not prescribed (Eussen et al. 2012). Surprisingly, ω 3 PUFAs cardioprotective effects are still observed in diabetic patients on statins (Kromhout et al. 2011), the same applies for the effects of ω 3 PUFAs heart rate (Kim et al. 2011), on plasmatic triglyceride level and on the threshold of occurrence of ventricular palpitations induced by electrical stimulation (Durrington et al. 2001; Schrepf et al. 2004; ORIGIN Trial Investigators et al. 2012). An inhibition of ω 3 PUFAs effects by statins cannot be simply explained by loss of efficiency of these lipids, which was demonstrated by the most recent clinical trials and meta-analysis. For example, in a diabetic population, it is possible to have a metabolic pathway altered by this pathology, which is sensitive to ω 3 PUFAs and not to statins and vice versa.

Also, patients included in randomized clinical trials (RCT) using ω 3 PUFAs can differ from the general population in an important way, which could explain the various results between RCTs (where there is intervention) and epidemiological studies. It was reported that patients who volunteered to join RCTs are frequently healthier and more active than the average population, which could affect the results in an unknown way. Furthermore, patients dropping out of the trials are often more ill and could be the ones benefiting most from ω 3 PUFAs.

Nutritionally, cooking method are of importance. Consuming boiled fish is associated with a lower rate of fatal arrhythmias when compared to fried fish consumption (Mozaffarian et al. 2003). Also, mortality linked to coronary heart disease was lower in individuals consuming oily fish as opposed to white meat fish or no fish at all (Oomen et al. 2000).

The AHA nutrition recommendations advise to limit oily fish consumption of children. Indeed, fat fishes, such as farmed salmon, swordfish, king mackerel, or tilefish, are

known to accumulate high levels of mercury, polychlorinated biphenyls, dioxins, organochlorines and other environmental contaminants (Hites et al. 2004). The levels of these substances are generally higher in older, larger, predatory fishes and marine mammals. Also, although a high rate of plasmatic DHA was associated with a reduction of the acute coronary artery events, this effect is significantly attenuated when increased levels of mercury are found in patient's hair (Rissanen et al. 2000), suggesting an interaction between ω 3 PUFAs and mercury. Also, it was suggested that a high intake of mercury from non-oily freshwater fish and the subsequent mercury accumulation in the body were associated with a higher an risk of myocardial infarction in Eastern Finnish men and this increased risk may be due to the promotion of lipid peroxidation by mercury (Salonen et al. 1995). More recently, Hu et al. (2016) studied the relationship between Canadian Inuit traditional diet and myocardial infarction risk in 2072 participants aged 18–79. They found that Inuit traditional diet contains high levels of EPA, DHA and mercury. A careful analysis of their results indicates that beneficial effects of EPA and DHA on myocardial infarction are diminished by the adverse effect of mercury (by 5% for men and 4% for women) (Hu et al. 2016). Thus, dietary mercury levels could partially explain certain contradictory results.

Finally, an important factor that is rarely taken into account in these studies is the inter-individual variability of incorporation of ω 3 PUFAs in cell membranes (Arterburn et al. 2006; Bougnoux et al. 2009). In 2010, it has been shown that cardioprotective properties of ω 3 PUFAs depend on their incorporation into cell membranes (von Schacky 2010), which suggests that positive effects needing incorporation can be masked in a sub-population which do not efficiently incorporate ω 3 PUFAs in their cell membrane.

Cellular parameters

The controversy about ω 3 PUFAs effects also extends to the cellular level (Billman 2013). The majority of electrophysiological single cell studies found an inhibition of ion currents such as fast sodium current (I_{Na}) (Xiao et al. 1995; Kang and Leaf 1996; Leifert et al. 2000), ultrafast activating delayed outward potassium current (I_{Kur}) (Honoré et al. 1994; Li et al. 2009), rapidly activating delayed rectifying outward potassium current (I_{KR}) (Guizy et al. 2005), L-type calcium current (I_{CaL}) (Xiao et al. 1997; Hazama et al. 1998; Rodrigo et al. 1999; Ferrier et al. 2002; Verkerk et al. 2006), and Na^+-Ca^{2+} exchanger current (I_{NCX}) (Xiao et al. 2004; Ander et al. 2007). On the other hand, ω 3 PUFAs were found to enhance slowly activating

delayed rectifying outward potassium current (I_{KS}) (Doolan et al. 2002) and outwardly rectifying potassium current (I_{TO}) (Macleod et al. 1998; Judé et al. 2003; Li et al. 2009). Also, incorporation of $\omega 3$ PUFAs has been positively correlated with mitochondrial proton leak (Hulbert 2003), and increased mitochondrial DHA content through lipid infusion or dietary intervention augments proton movement and state 4 respiration (Stillwell et al. 1997). In addition, DHA enhances Na^+ membrane permeability (Stillwell and Wassall 2003) and Na^+/K^+ -ATPase activity (Else and Wu 1999; Turner et al. 2003; Wu et al. 2004).

Collectively, these studies have led to the idea that $\omega 3$ PUFAs influence mitochondrial activity, and excitation–contraction coupling through modulation of ion channels. However, it is surprising that in a lot of epidemiological studies, if not all, no effects on electrocardiogram parameters were observed in agreement with such molecular effects as it is observed with drugs having comparable multi-ion channels effects.

Such contradictory and unspecific effects of $\omega 3$ PUFAs on ion membrane channels activity challenge the hypothesis that cardioprotective effects of $\omega 3$ PUFA could be due to the modulation of these channels or that in vivo, $\omega 3$ PUFAs have any effect on ion channels.

In parallel, some scientists were more interested in the regulation of intracellular Ca^{2+} , which is known to play a role in physio-pathological situations and to be a key actor in cardiac muscle and skeletal excitation–contraction coupling.

Acute application of $\omega 3$ PUFAs leads to numerous effects on intracellular Ca^{2+} and on cellular mechanisms that ensue from it (Judé et al. 2006; Billman 2012). Besides the fact that $\omega 3$ PUFAs inhibit many voltage-dependent calcium channels activity, it has also been shown that they inhibit pro-arrhythmic diastolic depolarization due to intracellular calcium elevation and this can be explained by a reduction of NCX exchanger activity (Szentandrassy et al. 2007; Berecki et al. 2007; Den Ruijter et al. 2008; Sankaranarayanan and Venetucci 2012).

$\omega 3$ PUFAs have direct effects on mechanisms that regulate sarcoplasmic Ca^{2+} level by decreasing Ca^{2+} released by the sarcoplasmic reticulum. Mechanistically, a decreased frequency of the occurrence of spontaneous calcium events (sparks) in isolated ventricular cardiomyocytes has been observed (Negretti et al. 2000; O'Neill et al. 2002; Honen et al. 2003; Sankaranarayanan and Venetucci 2012). In agreement with this observation, $\omega 3$ PUFAs reduce the opening probability of ryanodine receptor type 2 (RyR2), responsible for these calcium events (Swan et al. 2003). In 1993, Taffet observed that a $\omega 3$ PUFAs-enriched diet is associated with increased DHA incorporation in the cardiac sarcoplasmic reticulum membrane (Taffet et al. 1993). This effect is associated with a reduction of sarcoplasmic reticulum content and a decreased SERCA2a pump activity by

dietary interventions that change the composition, and possibly the structure of phospholipid membranes thereby affecting enzyme turnover. However, these observations are in contradiction with other studies (Leifert et al. 2000; Billman et al. 2012). It must be noted that the acute application of $\omega 3$ PUFAs induces an augmentation of the sarcoplasmic reticulum calcium content (Negretti et al. 2000; O'Neill et al. 2002; Swan et al. 2003). Also, delayed after-depolarization and early after-depolarization are both prevented by an acute or chronic exposition to $\omega 3$ PUFAs (Den Ruijter et al. 2008; Milberg et al. 2011).

In conclusion, $\omega 3$ PUFAs can regulate intracellular Ca^{2+} homeostasis, decreasing the risk of arrhythmias, in particular when these originate from a change of intracellular Ca^{2+} homeostasis such as during an ischemia/reperfusion episode (Billman 1991).

Dietary supplementation with $\omega 3$ PUFAs leads to their incorporation in cardiac membrane phospholipids. This incorporation in mitochondria, sarcoplasmic reticulum and cell membranes plays an essential role in the regulation of excitation–contraction coupling. Thus, several studies have investigated the effects of this incorporation. One important point is that after their incorporation, these lipids can undergo enzymatic and non-enzymatic oxidation, leading to new products derived from $\omega 3$ PUFAs. The effects of enzymatic metabolites such as prostaglandins or leukotrienes have been well studied (Calder 2010). However, it is important to note that in presence of a lipid antioxidant, alpha-tocopherol, the beneficial effects of $\omega 3$ PUFAs are totally abolished (such as anti-arrhythmic properties) whereas in presence of a pro-oxidant (low concentrations of hydrogen peroxide) enhancing non-enzymatic oxidation, the beneficial effects of these lipids are potentiated (Roy et al. 2015). This might be linked with a similar observation about the effects of DHA on rat ion currents (Judé et al. 2003). Recently, we focused our attention on certain non-enzymatic metabolites of $\omega 3$ PUFAs (NEO-PUFAs). We found that some NEO-PUFAs, namely the 4(RS)-4- F_{4t} -neuroprostanes and the 10(S)-10- F_{4t} -neuroprostane, can normalize RyR2 function and thus reduce the occurrence of abnormal extrasystoles (Roy et al. 2015). These results, and others, suggest that the beneficial effects of $\omega 3$ PUFAs can be obtained in conditions of oxidative stress (characteristic of many chronic pathologies).

Also, these discoveries open new perspectives for non-enzymatic oxygenated metabolites of $\omega 3$ PUFAs as potent healthy mediators in diseases associated with an oxidative stress (Burton et al. 1990; Janero et al. 1991; Sano 2010; Anderson and Taylor 2012; Anderson et al. 2012).

This element of oxidation must be taken into account, because it differs from one individual to another. The intensity of oxidative stress and antioxidant capacity are highly inter-individually different, thus even for a

comparable level of PUFAs, the production of NEO-PUFAs will be variable.

Conclusion

To conclude, all these contradictory data leads the scientific community to consider effects and cellular targets of ω 3 PUFAs (acutely or chronically applied).

Recently, it has been found that low ω 3 PUFAs blood level and dietary intake can potentially increase the risk of non beneficial outcomes and could explain the difference and the contradiction in the effects observed (Stark et al. 2016).

Many factors can explain the contradictory observations made in cells, animal and human studies as described in this review.

Therefore, it is important and essential to take into consideration these parameters in future studies that, otherwise, could generate other contradictory results. Notably, given the challenges of fatty acid analysis and reporting, an international initiative should be considered to lead to standardized approaches and methods before all studies. To limit the conflicting findings, a standardization of study method (taking into account dose and type of fatty acids, rate of oxidation) should be proposed such as the ω 3 PUFAs index proposed by Von Schacky (von Schacky 2010).

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