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The Role of Omega-3 Unsaturated Fatty Acids in the Modification of Arrhythmogenesis*

Rola nienasyconych kwasów tłuszczowych Omega-3 w modyfikacji procesu arytmogenezy

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Abstract

Over the past 30 years there has been an increasing interest in the role of polyunsaturated fatty acids (PUFAs) in reducing the risk of cardiovascular diseases. Omega-3 polyunsaturated fatty acids have anti-inflammatory, antiarrhythmic and anti-aggregating effects. They are used in the treatment of hypertension, hyperlipidemia and rheumatic arthritis. Recently, attention has been drawn to the antiarrhythmic effect of omega-3 acids, particularly DHA. However, numerous studies on animal models and observations in humans have not elucidated the mechanism of the antiarrhythmic effect of omega-3 acids. This study aims at presenting the mechanism and the role of omega-3 PUFAs in the modification of the arrhythmogenic process (*Adv Clin Exp Med* 2011, 20, 3, 385–390).

Key words: polyunsaturated fatty acids, heart, arrhythmias.

Streszczenie

Od 30 lat zwiększa się zainteresowanie badaczy rolą wielonienasyconych kwasów tłuszczowych (PUFA) w zmniejszaniu ryzyka chorób sercowo-naczyniowych. Wielonienasycone kwasy tłuszczowe omega-3 mają działanie przeciwzapalne, antyarytmiczne i przeciwaagregacyjne. Kwasy omega-3 stosuje się w leczeniu nadciśnienia tętniczego, hiperlipidemii i choroby reumatycznej stawów. Od kilku lat podkreśla się dużą rolę antyarytmicznego wpływu kwasów omega-3, zwłaszcza kwasu dokosaheksaenowego (DHA). Mimo wielu badań przeprowadzonych na modelach zwierzęcych oraz obserwacji u ludzi, mechanizm antyarytmicznego działania kwasów omega-3 wciąż nie jest do końca wyjaśniony. Niniejsze opracowanie ma przybliżyć mechanizm i rolę kwasów omega-3 w modyfikacji procesu arytmogenezy (*Adv Clin Exp Med* 2011, 20, 3, 385–390).

Słowa kluczowe: wielonienasycone kwasy tłuszczowe, serce, zaburzenia rytmu.

Interest in the therapeutic application of polyunsaturated fatty acids (PUFAs) for the prevention and treatment of cardiovascular diseases grew after a report published in 1976 indicating the role of increased sea fish consumption in reducing the risk of cardiovascular diseases [1]. Since then, numerous experimental studies involving animal models and randomized trials on patients with cardiac diseases have been conducted to define the therapeutic effect of PUFAs on cardiovascular diseases. As a result, the American and European Cardiologi-

cal Societies now recommend the consumption of sea fish at least twice a week or taking omega-3 acids (EPA + DHA) at a dose of 1000 mg per day. Such doses of omega-3 acids significantly reduce all-cause mortality rates as well as cardiovascular-related mortality rates [2].

In terms of chemical structure, PUFAs have been divided into two groups: omega-3 and omega-6 acids. Omega-3 acids have the first double bond between the third methyl and the rest of the molecule, while in omega-6 acids it is between the

sixth methyl and the rest of the molecule. Fish oils and algae are rich sources of polyunsaturated omega-3 fatty acids, particularly 20-carbon eicosapentaenoic acid (EPA) and 22-carbon docosahexaenoic acid (DHA). Polyunsaturated omega-3 and omega-6 fatty acids should be included in the diet or taken as supplements, because they are not synthesized by mammals. The exceptions are EPA and DHA, which may be synthesized in the body from 18-carbon alpha-linolenic (ALA) omega-3 acid (found in green vegetables, soya, nuts and sunflower), through the elongation and desaturation processes. DHA and EPA are precursors of prostaglandins, leukotrienes and thromboxanes, which have an anti-inflammatory, anti-aggregating and vasodilating effect. The role of EPA and DHA in reducing the concentration of triglycerides in the blood serum and the modification of the arrhythmogenic process [3–6] are also noteworthy.

The Mechanism of the Antiarrhythmic Effect of EPA and DHA

Despite numerous studies on animal models and cell cultures, the mechanism of the antiarrhythmic effect of EPA and DHA has not been fully explained. However, it is known that they reversibly modulate the effect of ion channels and converters in myocyte cell membranes [4, 7, 8]. It has also been found that DHA is preferentially built in cardiomyocyte membranes and that its concentration increases in a log-linear way. The content of ALA in the diet does not affect the content of DHA in the cardiomyocytes [9]. Long-term electrophysiological changes caused by omega-3 acids have not been studied yet. Verker et al. examined the changes in ion channels in the cardiomyocytes of cardiac ventricles isolated from swine after 8 weeks on a diet rich in fish oil, and found an increase in the density of potassium channels (I_{K1} , I_{Ks}) and a decrease in density of ion exchanger $Na^+ - Ca^{2+}$ I_{NCX} and L-type calcium channels ($I_{Ca,L}$) [10]. Other authors have reported a decrease in the density of sodium channels (I_{Na}) in isolated rat cardiomyocytes and HEK cells following the administration of omega-3 acids [11, 12]. An increase in the potassium current (I_{Ks}) in the repolarization phase, similarly to a decrease in I_{NCX} , contributes to a reduction in the action potential duration. A change in the density of I_{K1} may cause earlier repolarization and a more stable resting potential, which prevents the occurrence of delayed after-depolarizations (DADs). This is one of the potential mechanisms of omega-3 acids' antiarrhythmic effect [10]. A decrease in the density of

I_{NCX} may lower a predisposition to DADs. A shortening of the action potential duration after administering omega-3 PUFAs has also been observed in rabbits and guinea pigs [13, 14]. A shorter action potential duration may prevent reentry arrhythmias and early afterdepolarizations (EADs). Rabbits on a diet rich in omega-3 PUFAs showed a reduction in Torsades de Pointes tachycardia, which is often caused by EADs [15]. Additionally, a diet rich in omega-3 PUFAs may reduce the participation of β -adrenergic receptors in arrhythmogenesis and inhibit the activity of protein kinase A and calmodulin kinase II, which play an important role in the modulation of the functioning of ion channels [16, 17]. The inhibition of calmodulin kinase II activity may weaken the formation of EADs and, along with the suppression of calcium channels, may reduce their frequency.

Animal Studies

Numerous studies carried out on animals confirm the antiarrhythmic effect of omega-3 PUFAs. McLennan reported that rats on a diet rich in omega-3 PUFAs (fish oil) did not demonstrate any episodes of ventricular fibrillation during ischemia and reperfusion; but ventricular fibrillation was observed in 8% of the rats on a diet rich in omega-6 PUFA (sunflower seed oil) and in 36% of the rats on a diet supplemented by olive oil [8]. In a series of experiments conducted by Billman et al. on dogs in which ischemia was induced by closing the left anterior descending coronary artery and left circumflex artery, ventricular fibrillation was induced during a treadmill exercise test [18–20]. The intravenous administration of a 70% mixture of omega-3 acids (in which 33.9% was EPA and 25% was DHA) 60 minutes before the treadmill exercise test prevented ventricular fibrillation in seven out of eight dogs, while dogs that were intravenously administered an emulsion containing 7% ALA all suffered ventricular fibrillation. The dogs that got the mixture of EPA and DHA had a significantly lower heart rates before and during coronary occlusion; also, the PR interval increased significantly in ECGs after the mixture was administered [18]. In another experiment the emulsion with omega-3 acids was administered intravenously directly before left circumflex artery occlusion during the treadmill exercise test, and the infusion of free omega-3 PUFAs prevented ventricular fibrillation in 10 out of 13 dogs. The antiarrhythmic effect was associated here with lower heart rates, short QT intervals, decreased systolic pressure in the left ventricle, longer atrioventricular conduction times and prolonged PR intervals [19]. In

a third experiment, after infarction was surgically induced, the dogs were intravenously administered EPA or DHA a week before the treadmill exercise test. The administration of EPA prevented ventricular fibrillation in five out of seven dogs, and the administration of DHA prevented ventricular fibrillation in six out of eight dogs. Prior to the administration of DHA, all the dogs had been subjected to ventricular fibrillation stopped by defibrillation [20]. A study by Cunha et al. on electrical remodeling of atrial fibrillation in a dog model confirmed the effect of omega-3 PUFAs on the course of electric remodeling [21]. After the intravenous administration of omega-3 PUFAs (EPA and DHA) and rapid atrial pacing, the dogs had significantly longer effective refractory periods (ERPs) as compared with the control group. Rapid atrial pacing did not lead to atrial fibrillation in any of the dogs; nor were any changes in ECG parameters (P wave duration, PQ, PRS, RR or QTc intervals) observed [21]. That study confirms the findings of Xiao et al. that acute exposure to DHA and EPA reduces sarcolemmal sodium, calcium and potassium currents, and their observations of omega-3 PUFAs' effect on ERP [12].

Not all of the results of the studies on experimental models could be confirmed in randomized tests on humans, especially on people suffering from ventricular fibrillation and those with implanted cardioverter defibrillators (ICDs). This derives from the fact that studies conducted on large animal models are scarce and there are no studies on the effects of omega-3 PUFAs for longer periods of observation than several weeks. The duration of the antiarrhythmic effect has not been studied either. However, there have also been many studies confirming the results obtained from studies on animal models, including the biggest randomized trial to date – the GISSI-Prevenzione (GISSI-P) [29]. Studies on animal models have also led to a partial explanation of PUFAs' antiarrhythmic mechanisms. Ongoing studies will contribute to a fuller understanding of the mechanisms of polyunsaturated fatty acids and will help to explain the differences between the results from experimental studies and those from studies performed on humans with cardiac diseases.

The Use of Omega-3 PUFAs to Prevent Arrhythmias in Humans

The results of experimental studies showing PUFAs' significant effects in decreasing the frequency of potentially life-threatening arrhythmias

prompted researchers to investigate the possibilities of using PUFAs to treat people with cardiac diseases. The first observations concerning the effects of dietary omega-3 PUFAs on the rates of cardiovascular diseases were made in the 1970s [1]. It was found that the consumption of fish at least eight times a week in the diets of Greenland Eskimos and the Japanese was related to a significantly lower cardiovascular disease rate [1, 22]. These observations were confirmed by numerous randomized studies on the use of fish oil in patients with cardiac insufficiency; cardiovascular mortality rates decreased significantly among these patients after the application of omega-3 PUFAs. An analysis of some randomized studies carried out by Leon et al. showed that supplementation with fish oil reduced the number of sudden cardiac deaths from 45–48% to 25%, mainly thanks to the GISSI-P and JELIS studies [23]. In the GISSI-P, the death rate due to cardiovascular diseases decreased from 36% to 24% in patients whose diets had been supplemented with fish oil. This is connected with the stabilization of atheroma by omega-3 PUFAs through reduction of the inflammatory process, inhibition of lipoprotein lipase within the atheroma and reduction of cholesterol LDL fraction. The antiarrhythmic effect of omega-3 PUFAs was also confirmed in patients with left ventricle insufficiency and numerous premature ventricular beats (VPs) [24]. In this group of patients, VPs decreased on average from 10956 VPs/24 h to 9112 VPs/24 h. This study showed that the application of omega-3 PUFAs (700 mg of EPA and 560 mg of DHA in 24 h) in patients with cardiac insufficiency, regardless of the reason, led to a significant reduction in heart rate, which translates into a significant reduction in the risk of sudden cardiac death [24].

The SOFA study [25] involved a very diversified group of patients, and omega-3 PUFAs were administered via a diet containing fish or seafood, at a dose of 8 g of omega-3 PUFAs a month. The first ICD intervention or the patient's death were taken as the primary endpoint; ICD intervention was noted in 30% of the patients, and 5% of the patients died. A substudy of the GISSI-HF trial [26] found that patients with ICDs who were given omega-3 PUFAs had decreased ventricular fibrillation (VF) and ventricular tachycardia (VT) episodes as compared with the control group. A study performed by Christensen et al. concluded: "Patients with a low content of n-3 PUFA in the serum had a higher incidence of ventricular arrhythmias compared with the patients with high serum levels of n-3 PUFA. The data suggests that the protection offered by n-3 PUFA against sudden cardiac death observed in previous studies is mediated by

a direct antiarrhythmic effect of n-3 PUFA" [27]. Brouwer et al. conducted a meta-analysis of three trials investigating fish oil and ventricular arrhythmia, and concluded that the results "do not support a protective effect of omega-3 PUFAs from fish oil on cardiac arrhythmia in all patients with an ICD. Current data neither prove nor disprove a beneficial or a detrimental effect for subgroups of patients with specific underlying pathologies" [28]. In the GISSI-P trial it was found that treating patients with myocardial infarction with omega-3 PUFAs significantly lowered mortality, non-fatal myocardial infarction, and stroke [29].

Despite earlier experimental results showing their positive effect on electrical ventricular remodeling, the efficacy of PUFAs in preventing incidents of ventricular fibrillation, has not been confirmed. A recent meta-analysis of the results of randomized clinical trials found no statistically significant impact of PUFAs on the prevention of ventricular fibrillation, although the authors added that a "large-scale trial with higher doses and longer follow-up might be required to rule out the possibility of any treatment benefit" [30]. A prospective, randomized multicenter trial evaluated the safety and efficacy of prescribing omega-3 fatty acids to prevent recurrent symptomatic atrial fibrillation (AF) in patients with symptomatic paroxysmal or persistent AF, without structural heart disease [31]. During the first seven days the participants in the study were given a priming dose of 8 g per day of omega-3 or placebo, and then 4 g per day through the 24th week of the trial. Each 1-g PUFA capsule contained 465 mg of EPA and 375 mg of DHA. Every other week the symptoms of AF recurrence were monitored by telephone. In cases of a primary endpoint incident (the first recorded AF recurrence or atrial flutter) the necessary procedures were implemented to restore correct sinus rhythm. Although the average heart activity at the first AF recurrence or atrial flutter was significantly lower in the group receiving medica-

tion, in the 24th week of the trial the differences between the two groups' parameters compared to their initial state were not statistically significant; the use of PUFAs did not reduce the incidents of symptomatic AF among the patients in the study [31]. In another study it was confirmed that omega-3 PUFAs reduced the relative risk of hospitalization for AF in patients with myocardial infarction and was also associated with a reduction in all-cause mortality [32].

The diversity of recommended doses of omega-3 PUFAs and their varying content in different fish species can make it difficult to compare and analyze studies, and this contributes to the difficulties in interpreting the results obtained in animal studies and in those involving humans. The GISSI-Prevenzione study was the only one to use an 850-mg dose of a standardized preparation of DHA and EPA, and it demonstrated that omega-3 PUFAs significantly reduced mortality due to sudden cardiac death in patients surviving recent myocardial infarction [29].

Summarizing the studies on the influence of PUFAs on arrhythmogenesis, its significant role in modifying the process and reducing arrhythmia – especially ischemic arrhythmia – should be emphasized. In the GISSI-P and GISSI-HF studies, the advantage of using omega-3 ethyl esters in patients recovering from heart infarcts and heart failures was confirmed. At present there is no convincing evidence that omega-3 acids are effective in patients with ICDs due to reasons other than ischemic heart disease. There is also no evidence that PUFAs reduce the frequency of ventricular fibrillation recurrence, although longer studies on larger patient populations are needed.

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