Vascular Pharmacology 82 (2016) 11–19

Contents lists available at ScienceDirect

Vascular Pharmacology

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

Review

Marine omega-3 highly unsaturated fatty acids: From mechanisms to clinical implications in heart failure and arrhythmias

Tobias Glück [a,b,*], Peter Alter [a,*]

[a] Department of Medicine, Pulmonary and Critical Care Medicine, Philipps University, Marburg, Germany
[b] Department of Medicine, Cardiology and Angiology, AGAPLESION Evangelisches Krankenhaus Mittelhessen, Gießen, Germany

ARTICLE INFO

Article history:
Received 21 October 2015
Received in revised form 12 March 2016
Accepted 29 March 2016
Available online 11 April 2016

Keywords:
HUFA
Polyunsaturated fatty acids
Omega-3
EPA
DHA
Heart failure
Ventricular wall stress
Coronary artery disease
Arrhythmia
Pericardium
Atrial fibrillation
ICD
SCD
Atherosclerosis

ABSTRACT

Therapeutic implications of marine omega-3 highly unsaturated fatty acids (HUFA) in cardiovascular disease are still discussed controversially. Several clinical trials report divergent findings and thus leave ambiguity on the meaning of oral omega-3 therapy. Potential prognostic indications of HUFA treatment have been predominantly studied in coronary artery disease, sudden cardiac death, ventricular arrhythmias, atrial fibrillation and heart failure of various origin. It is suspected that increased ventricular wall stress is crucially involved in the prognosis of heart failure. Increased wall stress and an unfavorable myocardial remodeling is associated with an increased risk of arrhythmias by stretch-activated membrane ion channels. Integration of HUFA into the microenvironment of cardiomyocyte ion channels lead to allosteric changes and increase the electrical stability. Increased ventricular wall stress appears to be involved in the local myocardial as well as in the hepatic fatty acid metabolism, i.e. a cardio-hepatic syndrome. Influences of an altered endogenous HUFA metabolism and an inverse shift of the fatty acid profile was underrated in the past. A better understanding of these interacting endogenous mechanisms appears to be required for interpreting the findings of recent experimental and clinical studies. The present article critically reviews major studies on basic pathophysiological mechanisms and treatment effects in clinical trials.

Contents

* Corresponding authors at: Department of Medicine, Pulmonary and Critical Care Medicine, University Medical Center Giessen and Marburg, Philipps-University Marburg, Baldingerstrasse, 35033 Marburg, Germany.
E-mail addresses: tobias.glueck@uni-marburg.de, tobias_glueck@gmx.de (T. Glück), alter@uni-marburg.de (P. Alter).

http://dx.doi.org/10.1016/j.vph.2016.03.007
1537-1891/

1. Introduction

Early optimistic expectations on beneficial effects of marine omega-3 fatty acid therapy in cardiac disease gradually declined during the last years. Due to ambiguous findings of several studies, recommendations regarding the therapeutic use of oral omega-3 therapy in heart disease are very reluctant. Nevertheless, there is a variety of promising data from basic research on omega-3 fatty acid actions. Potential inconsistencies and limitations of clinical trials need to be addressed before interpreting their findings. The present article will focus on basic mechanisms and clinical data as derived from contemporary large clinical trials.

1.1. A brief biochemical overview

Since in 1956 Sinclair described a relationship between a high fat diet rich in marine omega-3 fatty acids of a Greenland Eskimo population and low incidence of coronary artery disease, there is an increasing interest in polyunsaturated fatty acids (PUFA) [1–3]. Consecutively, numerous studies on basic research revealed manifold mechanisms and molecular actions of these long chain carbons with their characteristic double bonds. In mammals, there are only unbranched fatty acids with an even number of carbons. The medical nomenclature is not synonymous with the chemical name. Therefore, the position of the first double bond, counted from the "omega"-called methyl end, is crucial for classification and constitute for the popular name of omega-3 (n − 3) fatty acids (Fig. 1).

The endogenous metabolisms comprise mitochondrial and cytoplasmic elongases (Elovl) catalyzing the carbon chain extension and endoplasmic desaturases inserting double bonds in cis configuration. Since mammals cannot insert double bonds beyond the ninth carbon, Linoleic acid (18:2n − 6) and α-Linolenic acid (18:3n − 3) are essential for humans and thus have to be incorporated by the diet. In the presence of required precursors, e.g. after consuming a fatty fish meal, omega-6 and omega-3 polyunsaturated fatty acids (PUFA) undergo a metabolizing pathway as shown in Fig. 2. Because of their outstanding physiological role, in the following text the PUFA beyond arachidonic acid (20:4n − 6, AA) and eicosapentaenoic acid (20:5n − 3, EPA) are referred as highly unsaturated fatty acids (HUFA) [4].

The metabolism of elongation and desaturation (Fig. 2) is well described [5–7]. However, the last step of the synthesis of docosahexaenoic acid (22:6n − 3, DHA) (Fig. 1) and docosapentaenoic acid (22:5n − 6) remains challenging. In the endoplasmic reticulum, the direct precursors 24:6n − 3 and 24:5n − 6 are known to be produced and transported via carnitine octanoyltransferase, a family member of carnitine acetyltransferases, into the peroxisomes for removal of two carbon atoms [8]. Ambiguity exists on the role of the beta-oxidation as source of energy provider on the one hand and a key-step of 22:6n − 3 metabolism on the other [9]. Therefore it remains challenging how synthesis and degradation of DHA in the same cell compartment is regulated.

Besides the endogenous metabolism, which basically takes place in the liver as central metabolic organ, the distribution and incorporation of HUFA in the human organism is of interest. In focus of HUFA action is the brain (neurological disorders), the adipose tissue and the myocardium. It has been suggested to assess the red blood cell content as surrogate marker of cardiac omega-3 fatty acids [10]. Harris and von Schacky described the EPA and DHA concentration as percentage of total fatty acids using the term "omega-3 index" [11]. A bundle of dietary studies with supplementation of EPA and DHA shows that predominantly DHA (more than other HUFA) is incorporated in myocardial phospholipids [12]. Accordingly, the question of a potential selective uptake mechanism arose, and endogenous metabolism and clinical consequences were envisaged as target of further studies. [9]. There is an emerging evidence that adipose tissue, the substrate of obesity and succeeding comorbidities including the metabolic syndrome, is mediating beneficial effects of n − 3 HUFA [13]. Among others, it was shown that EPA and DHA influence the adipose tissue metabolism including adipocyte glucose utilization and insulin sensitivity. In particular, adipokines, which are crucially involved in glucose and lipid metabolism, were shown to interact with HUFA. In experimental obese animals, we recently demonstrated a decreased EPA and DHA concentration in adipose tissue, which was paralleled by an increase of n − 6/n − 3 ratio of total fatty acids [9]. A review of current literature is provided by Martínez-Fernández et al. [13].

2. Basic mechanisms and clinical implications

2.1. Antiarrhythmic actions

Several beneficial antiarrhythmic effects of omega-3 highly unsaturated fatty acids have been shown in animal studies on monkeys and rats after induction of ventricular fibrillation, which is in contrast to less or no effects of omega-6 HUFA [14–16]. Numerous studies explored electrophysiological mechanisms of omega-3 fatty acids, predominantly focused on DHA. A detailed overview provides the review by McLennan [17].

HUFA are commonly bonded into the inner position (sn − 2) of phospholipids. However, the esterified storage state appears not to protect cardiomyocytes from arrhythmias [18]. Triggered by an increased sympathetic activity, e.g. due to myocardial ischemia, HUFA were released by phospholipase A2 [19] and incorporated into the cell membrane with influences on their fluidity [20]. Ion channels undergo allosteric changes when HUFA are integrated into their microenvironment. Leaf and Xiao et al. described an increasing electrical stability of the cardiomyocyte, which predominantly results from fast voltage dependent sodium channels and inhibition of L-type calcium channels [21–24].

In an interesting experimental study, Beig et al. described an improved electrical stability of the myocardium following physical exercise training as indicated by higher doses of the pro-arrhythmic drug aconitin required to induce ventricular arrhythmias in running rats [25]. The authors particularly discussed vagal and sympathetic influences. Also, an enhanced electrical stability by modulated ion channels due to increased HUFA could provide a further explanation. Recently, we found a 24.6% increase of DHA in LV myocardium of voluntary wheel running rats, most probably due to an increased energy production of the myocardium associated with an enhanced beta-oxidation required for the running exercise [9].

Another aspect of antiarrhythmic actions is an impaired autonomic tone, in particular a decreased heart rate variability, which is associated with an increased risk of arrhythmias in patients with congestive heart failure [26] and increased cardiac mortality after myocardial infarction (MI) [27]. Depression of heart rate variability was shown to be associated with increased ventricular wall stress [28,29]. Supplementation of n − 3 HUFA potentially exhibits favorable prognostic effects by an increase of the heart rate variability [30–32]. For further information on

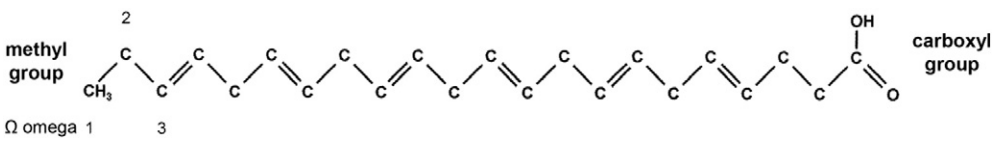

Fig. 1. Constitutional formula of docosahexaenoic acid (DHA, 22:6n − 3). The number of carbons from the methyl end to the first double bond (omega-3, n − 3) is eponymous.