ELSEVIER

Journal of Cystic Fibrosis 4 (2005) 27–34

Journal of Cystic Fibrosis

www.elsevier.com/locate/jcf

Review article

Docosahexaenoic acid trials in cystic fibrosis: A review of the rationale behind the clinical trials

S. Van Biervliet*, J.P. Van Biervliet, E. Robberecht, A. Christophe

Cystic Fibrosis Centre UZ Ghent, Ghent University Hospital, Belgium

Received 27 August 2004; accepted 8 November 2004

Keywords: Cystic fibrosis; Docosahexaenoic acid; Omega-3 fatty acids; Inflammation

Contents

1. Introduction

Cystic fibrosis (CF) is the most common lethal genetic disease in Caucasians. The cystic fibrosis gene codes for an integral membrane protein, the cystic fibrosis transmembrane conductance regulator (CFTR). It is a cAMP-dependant chloride channel with the capacity of not only excreting organic anions as glutathione and cytochrome P450 metabolites conjugated to glutathione but has also other regulatory functions [1]. Some of the most important symptoms of CF are not directly the consequence of impaired chloride transport. The pulmonary inflammation and infection resulting in pulmonary failure is the major cause of death. Different medications have been used to

Abbreviations: CF, cystic fibrosis; $iPLA_2$, intracellular calcium-independent; CFTR, cystic fibrosis transmembrane conductance regulator; $sPLA_2$, secretory PLA_2; FA, fatty acid; $cPLA_2$, cytosolic PLA_2; DHA, docosahexaenoic acid; COX, cyclooxygenase; EFA, essential fatty acid; PG, prostaglandin; PUFA, polyunsaturated fatty acid; TX, thromboxanes; PLA_2, phospholipase A_2; PGI2, prostacyclin; LA, linoleic acid; LOX, lipoxigenase; AA, arachidonic acid; LTs, leukotrienes; EPA, eicosapentaenoic acid.

* Corresponding author. Paediatric Gastroenterology, Ghent University Hospital, De Pintelaan 185, 9000 Ghent, Belgium. Tel.: +32 9 2403699; fax: +32 9 240.

E-mail address: stephanie.vanbiervliet@ugent.be (S. Van Biervliet).

doi:10.1016/j.jcf.2004.11.001

influence the inflammation as antibiotics, steroids and non-steroidal anti-phlogistics, antioxidants... resulting in an important gain of life expectancy.

Recent studies give however new insights in the possible pathophysiology of the increased sensitivity for inflammation of CF patients. Especially the role of the metabolism of fatty acids (FAs) is highlighted by recent findings in CFTR −/− mice. Freedman et al. described a mouse model of CF in which important abnormalities of the FA metabolism were shown [2]. The biochemical aberrations were corrected by oral supplementation of pharmacological doses of docosahexaenoic acid (DHA, 22:6ω3). This results in new therapeutic perspectives. The first clinical DHA supplementation trials have already started. This review goes into the possible rationale behind these trials. A brief overview of the metabolism of the essential fatty acids (EFAs) is given.

2. Essential fatty acids and their metabolism

FAs as triglycerides and phospholipids are the main components of energy production and storage. After digestion, absorption and biosynthetic transformations, acyl chains are not only used for triglyceride synthesis but also become part of biomembranes after esterification to complex lipids. FAs account for more than 50% of the molecular mass of phospholipids. The fatty acid tails of the phospholipids are responsible for the apolar nature of membrane bilayers. The phospholipid membrane components influence many membrane functions as ion channelling and transport, endo- and exocytosis and the functions of membrane-associated receptors and enzymes [3].

Polyunsaturated fatty acids (PUFAs), originating from EFAs by elongation and desaturation, are precursors of biologically active molecules, the eicosanoids and docosanoids. PUFAs contribute to the control processes of nuclear transcription, via special receptors and response elements [4,5]. PUFAs released by agonist stimulated phospholipase A_2 (PLA_2), are involved in signal transduction [6]. Moreover they are involved in activation or modulation of protein kinase C, in direct stimulation of membrane receptors and in interaction with guanylate cyclases. They also participate in translocation processes of biosynthetic key-enzymes. A diversity of acyl chains may be required to fulfil so many different tasks [4–6].

3. Interconversion of long-chain PUFAs

De novo synthesis of FAs produces mainly palmitate (C16:0), with minor amounts of stearate (C18:0). Many cells have the capacity for 2-carbon chain elongation of FAs that takes place mostly in the endoplasmatic reticulum. It is the main source of acyl chains greater than 16 carbon atoms in membrane phospholipids.

All eukaryotic organisms contain polyenoic fatty acyl chains in their membrane lipids. Most tissues can modify acyl chain composition by introducing double bonds by means of desaturases (Δ5, Δ6, Δ9). Linoleic acid (LA, 18:2ω6) and α-linolenic acid (18:3ω3) are EFAs. These acyl chains are converted into other FAs containing 3 to 6 double bonds (Fig. 1). Arachidonic acid (AA, 20:4ω6), an ω6 FA found in most tissues, can be formed from LA by alternating sequence of Δ6 desaturation, chain elongation of the 18:3ω6 intermediate thus formed and Δ5 desaturation of 20:3ω6 (Fig. 1). AA is a component of phospholipids contributing to structural integrity of membranes and is the primary precursor of several classes of oxygenated derivatives.

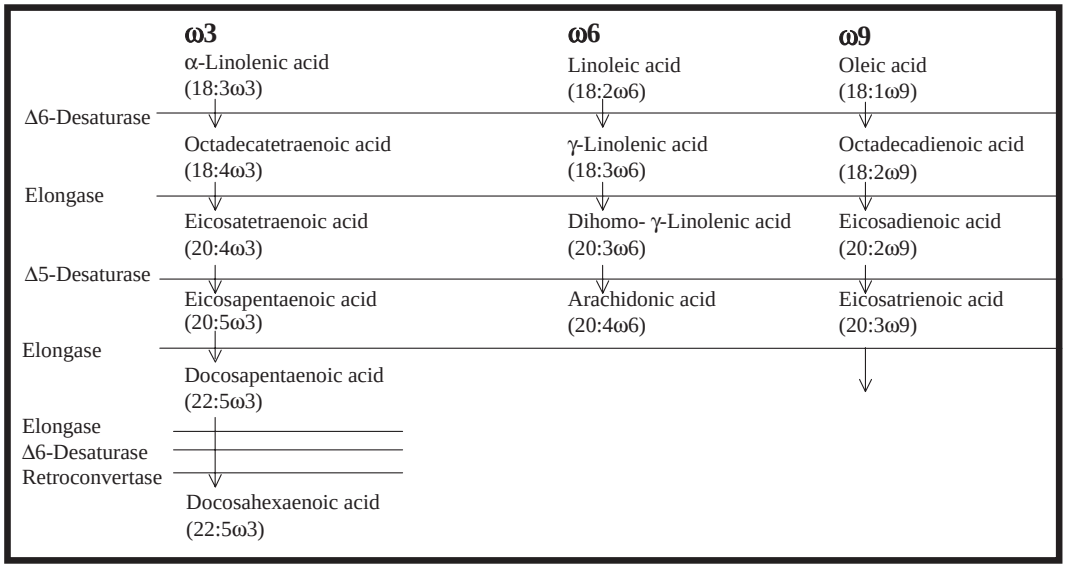

Fig. 1. Fatty acid notation: number of carbon atoms: number of double bonds followed by biochemical series.