Developmentally Dependent and Different Roles of Fatty Acids OMEGA-6 and OMEGA-3

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Received February 9, 2011; Accepted April 18, 2011.

Key words: PUFA-OMEGA-6 – PUFA-OMEGA-3 – Brain development – Immunity

Abstract: The developmentally-dependent differences in the biological significances and effects of PUFA-OMEGA-6 (namely of arachidonic acid) and PUFA-OMEGA-3 (namely of docosahexaenoic acid) are discussed. The clinical results as well as developmental experiences are indicating a hypothesis of the evolution that created mutual relationship between those two substances (with immunological basis and following recuperation). The anti-inflammatory actions of PUFA-OMEGA-3 are the most visible (and significant) contrasts as compared with the large affects of namely arachidonic acid and its metabolites.

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Developmental aspects

According to textbook images of lineages of fatty acids, the PUFA-OMEGA-6 represents the last but one line and the PUFA-OMEGA3 appears to be the last line (as listed at Figure 1).

It is remarkable that we found this scheme and the configuration in particular extend during the monitoring of development changes in representation of various fatty acids (and appropriate groups) in mammal's organism. Nowadays we have lots of data on the fact that during the postnatal development of mammals the concentration of fatty acids, especially in the line OMEGA-3, gradually increases in the blood, in many organs and in many tissues (Figure 2a and b). This applies for the serum of laboratory rats in the fraction of non-esterified fatty acids. The representation of docosahexaenoic (DHA) acid is increasing in the tissue of cerebral cortex from birth to adult age up to 20% of all available fatty acids. In the tissue of medulla oblongata (so in a phylogenetically very old brain region) is the participation of DHA contrariwise oscillating over 5–6%, during the postnatal development. Nevertheless, the representations of DHA in neocortex and medulla oblongata during the 5th day of postnatal life are the same (Figure 3) (Mourek et al., 1986; Šmídová et al., 1990; summarily Mourek, 1995, 2007, 2009).

Evident developmental trend can also be found in humans: we have proved existence of a highly significant correlation between the birth weight and concentration of PUFA-OMEGA-3 in the blood serum of new-borns (Mourek and Dohnalová, 1996).

Similarly the data from neonatology clinics demonstrate changes in the spectrum of fatty acids (serum) in cases of various developmental retardation (early births, prematurity, hypotrophy) or in other high-risk states (gestational diabetes, use of adrenergic tocolytics). It is possible to detect a significant decrease of PUFA-OMEGA-3 in all of indicated cases which is buffered by the increase of amounts of saturated fatty acids which have generally shorter descriptor (Šmídová et al., 1993; Mourek et al., 1995, 1998, 1999; Mourek and Koudelová, 1997). Stress brings similar effects by the mechanism of lipoperoxidation after which a significant depletion PUFA-OMEGA-3 occurs (above all the DHA acid).

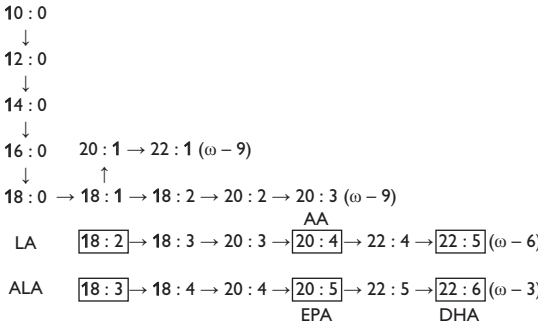

Figure 1 – The simplified scheme of particular lines of fatty acids. (AA – arachidonic acid; DHA – docosahexaenoic acid; EPA – eicosapenatenoic acid; LA – linoleic acid; ALA – linolenic acid)

PUFA-OMEGA-6 is also affected by the above listed clinical manifestations, only in a smaller scale (Mourek et al., 2005; recapitulation Mourek, 2009). Similarly develops the body balance in the group of monoenoic fatty acids. Both groups have certain rigidity or resistivity. Among the indirect evidences of the very significant relationship between the process of maturation and PUFA-OMEGA-3 concentration (above all with the last link DHA), very important is the inherence in the breast milk. In colostrum the proportion between arachidonic and docosahexaenoic acid is 1:1 (!) (Mydlilová et al., 1992, 1993; recapitulation Mourek, 2007, 2009).

This brief review on the developmental changes in organism and relationship of such development and fatty acids PUFA-OMEGA-3 concentration allows making several statements:

1) PUFA-OMEGA-3 is integrally related to the developmental changes in the mammalian organism.

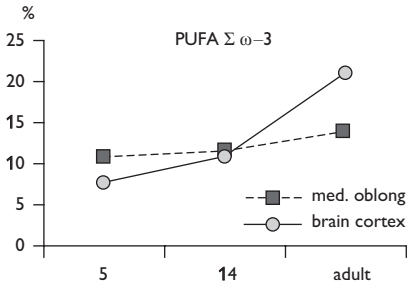

Figure 2a – Participation of polyunsaturated fatty acids OMEGA-3 in the brain cortex (full line) and in medulla oblongata (albino rats – Wistar), expressed as % of total fatty acid measured. (x-axis – age in postnatal days; adult)

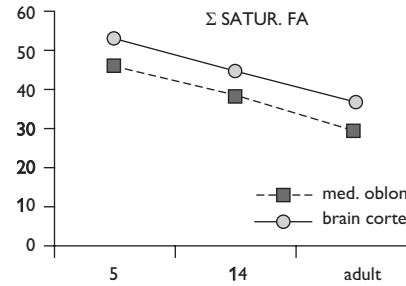

Figure 2b – The participation of saturated fatty acids in the brain cortex and medulla oblongata (albino rats – Wistar). (legend description see Figure 2a)

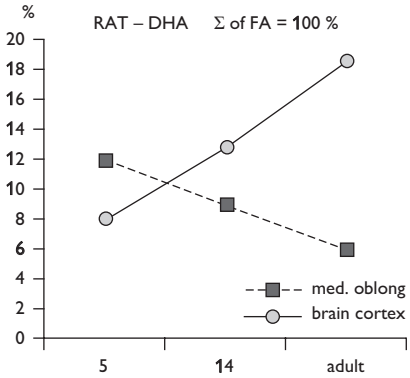

Figure 3 – The participation of docosahexaenoic acid in the brain cortex and medulla oblongata (albino rats – Wistar). (legend description see Figure 2a)

2) In the tissue of cerebral cortex the portion of DHA in adult age (laboratory rat – Wistar) represents about 20% and the portion of AA (arachidonic acid) is about 10% from all detected fatty acids. In the phylogenetically older parts is the portion of DHA evidentially smaller.
3) There is a significant relation between the birth weight of newborn and the portion of PUFA-OMEGA-3 in the blood serum.
4) In all conditions when the development of organism is compromised (malnutrition, morbidity etc.), concentration of PUFA-OMEGA-3 in the blood serum decreases. Along with it, concentration of saturated fatty acids – above all of those which have a shorter chain, rapidly increases.
5) The initial developmental stages of mammalian organism are characterized by higher fraction of saturated fatty acids.

Clinic

Though evolutionary aspect is very important for the hypothesis presented in this work – the different evolutionary functions of unsaturated fatty acids OMEGA-6 and OMEGA-3 – the extensive clinical experience is important too.

It is commonly known that DHA (in smaller amount EPA too) as a dietary supplement improves various diseases at clinical, laboratory and subjective levels (Neuringer et al., 1988; Crawford, 1993; Das, 2003, 2004; Ristic and Ristic, 2003; Harris, 2005, 2007; Mourek, 2005; Žák et al., 2005). It regards mainly cardiovascular diseases, where DHA has positive effects on hypertension, it is used in prevention or for the improvement of heart failure and arteriosclerotic vascular disease, heart arrhythmias, regeneration of vascular endothelium, processes of blood rheology, diabetic dyslipidemia (Zeman et al., 2005) or it decreases the risk of thrombogenesis (Simopoulos, 1991; recapitulation Seo et al., 2005). The possible relation between the absence (or presence) of PUFA-OMEGA-3 and metabolic syndrome was several times considered and discussed (Mourek, 2005, 2008; Sener et al., 2009; Carpentier et al., 2010).

PUFA-OMEGA-3 is known to effect immunity and supplementation of organism by DHA and EPA (eicosapenatenoic acid) was proved to increase the resistance to autoimmune diseases. Improvement after the administration was referred to diabetes, insulin resistance, atopy, allergic diseases and post operational states or complications. One of the most important and many times approved finding is that the DHA significantly inhibits the activation of proinflammatory cytokines (TNF alpha, IL-1, IL-6) (Liu et al., 2003).

Supplementation the organism by OMEGA-3 decreases the progress of cognitive functions and memory loss in Alzheimer's disease, dementia and arteriosclerotic vascular disease (Simopoulos, 2002; DeLorgeril, 2007; Lu et al., 2007; Pérez-Matute et al., 2007; Boudruault et al., 2009; Riediger et al., 2009; Sales et al., 2009; Raboch, 2010).

There are no similar indications for PUFA-OMEGA-6.

PUFA-OMEGA-6: relation to PUFA-OMEGA-3

PUFA-OMEGA-6 is mainly mentioned by nutritionists due to the high participation in our common diet and significantly exceeds the generally recommended proportion between intake of PUFA-OMEGA-6 and OMEGA-3. The ration between linoleic acid (LA) ($18:2_{n-6}$) and linolenic acid (ALA) ($18:3_{n-3}$) is often referred in literature and it was determined as 5:1 (1.5 g LA/0.3 g ALA/adult/24 hours).

In most of the European countries and in the USA, the above mentioned ration was found to be shifted in advantage of PUFA-OMEGA-6. Recent measurements in the Czech Republic (in the central Moravia) have shown the value at the level of 16:1 (Rataj, 2010).

Such disproportion is considered to be one of the most important disbalances in organism representing high morbidity risks (Harris et al., 2009). We assume that the mentioned recommendations have general character and do not respect the whole spectrum of organism's requirements.

Increase in the proportion of OMEGA-6 intake/OMEGA-3 is clearly connected to the risk of compromised immunity and a higher risk of autoimmune diseases (Korotkova et al., 2004) in contrast to the sufficient amount of EPA and DHA (together with vitamin E) which is considered as the base for the development of immune system (Babcock et al., 2002; Ergas et al., 2002; Calder, 2003; Harbige, 2003). The presence of OMEGA-3 fatty acids in the organism is not only a prevention for various diseases, but is also considered to be a correction mechanism and physiological regulation of immune system (Grimm et al., 2002; Weiss et al., 2002).

Permanent predominance of PUFA-OMEGA-6 in organism, especially the most important arachidonic acid ($20:4_{n-6}$), brings about an increased production of leucotriens A, B, C etc. with an index 4, prostaglandins and thromboxans (TXA_2). Above mentioned leucotriens with the index 4, manifest proinflammatory effects (with certain exception). For instance LTB_4 increases vascular permeability, activates leucocytes, causing hypersensibility with vasodilatative effects. The LTB_4 is often called an "inducer" of proinflammatory reactions. Thromboxane TXA_2 significantly increases the risks of thrombocytes aggregation. Thus, the above mentioned leucotriens formed by processing of arachidonic acid, have similar effects as yet many times discussed proinflammatory cytokines. Their effects can therefore potentiate.

Leucotriens for which the initial substrate is arachidonic acid are in certain contrast with the leucotriens produced by metabolic pathways from the eicosapentaenoic acid (EPA) ($20:5_{n-3}$). These leucotriens possessing index 5 show much smaller proinflammatory effect (Harris et al., 2009). In addition, the thromboxane formed from this same substrate is more potent inhibitor of dissipation of arachidonic acid from the plasmatic membranes. Thus, the risk resulting from the excess of the leucotriens with the index 4 becomes smaller.

These findings are equivalent with our previous findings: PUFA-OMEGA-6 support the activity of proinflammatory cytokines, accelerate pro-arteriosclerotic processes, even show carcinogenic effect and they do it directly or through some of the arachidonic acid metabolites (Mourek, 2009). Positive effect of PUFA-OMEGA-3 was also proved at the mitochondrial level – in the process of oxidative phosphorylation (Hulbert et al., 2006).

We are aware of certain simplification: the arachidonic acid has in the organism also positive effects and for instance prostaglandins participate or evoke several physiological processes (Čertíková and Chábová, 2008). However, liberation (by phospholipase-PLA_2) of the arachidonic acid from the plasma membrane (the absolute or relative overload) always means above the mentioned risk. Moreover there is another usually ignored risk: both overload of saturated fatty acids and PUFA-OMEGA-6 acids significantly inhibit the activity of fatty acid desaturases in the cascade of linolenic acid – thus causing a lack of EPA and DHA (even with relative sufficiency of ALA). The above mentioned enzymatic processes of PUFA-OMEGA-3 are also sensitive to the changes of internal environment such as hyperglycemia, disturbances of ionic balance etc.

Interpretation

Mechanisms of beneficial and protective effect of mainly DHA, as well as interpretations of physiological functions of both groups of PUFA are not yet definitely determined.

With regard to our long research in this area, we presume to set following concept – there are probably two mutually interconnected mechanisms:

(1) DHA is a component of cytoplasmic membrane. Its role and importance in cytoplasmic membrane, or in intracellular membranes, is not accidental but it is result of evolutionary processes. Thanks to its 6 double bonds and 7 carbon atoms, the molecule of DHA can form an unusual number of spatial variations.

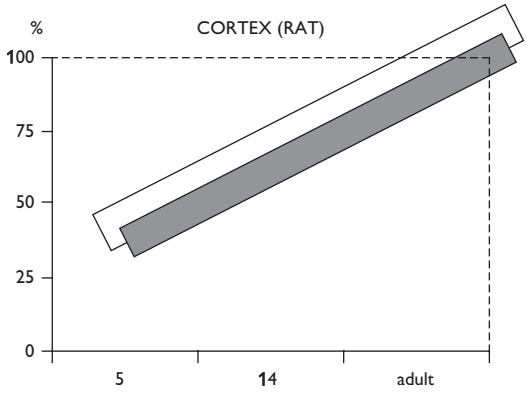

Figure 4 – The developmentally changes (expressed in %) of the Na^+-K^+-dependent ATPasa and the participation of docosahexaenoic acid in the brain cortex. (white column – DHA; grey column – Na^+-K^+-dependent ATPasa; x-axis – age in postnatal days; A – adult)

In the case of rotational movement, as well as in the case of double bond (*cis*), the distance between two carbon atoms becomes shorter (from 3.84 to 3.16 Å). Multiple spatial variations happen in this way due to these flections. We previously introduced this concept (Mourek, 1999, 2005).

According to our opinion, this spatial variability has a crucial importance: it represents the possibility to encompass and anchor functional proteins in cytoplasmic membrane. Function of receptors, ion channels etc. is not only the question of their presence or quality, but also the result of adequate interaction with components of plasmatic membrane. Orientation and arrangement of such functional proteins is causally linked to the architecture of lipid bilayer where they were implanted during development.

When we look at activity of dominant enzymes for functioning of mammal cell as for example Na^+-K^+ dependent ATPase and analogically on representation of DHA, then we find very similar trends (brain cortex of laboratory rat – Wistar) (Figure 4) (Mourek and Šťastný, 1978).

(2) The second important and recently discovered feature of DHA molecule is the ability to modify gene expression (in smaller extent it is true also for EPA and ALA). Research was focused mainly on the nervous tissue (Kitajka et al., 2002; Kothapalli et al., 2007), but the same was found also in liver cells (Swagell et al., 2007) and some other tissues (Brouard and Pascaud, 1999; Miyaoka et al., 2001; Lapillonne et al., 2004). Researchers confirmed effects of DHA at 55 genes so far. Changes induced by DHA altogether apply to important processes as for example expression of some ion channels, synaptogenesis, and plasticity. The inhibitory effect of DHA on gene expression was found in more than 40 genes.

Similarly to experimental data, also clinical observations can predict how extensive this field is. DHA (and also EPA) inhibits growth of breast carcinoma conclusively but application of PUFA-OMEGA-6 has exactly opposite effect at the same time (!) (Hammamieh et al., 2007). A similar work in prostate cancer is published by Chung et al. (2001). Protective effect of DHA on carcinogenic processes (tested on oncogenes), was confirmed as well (Menendez et al., 2004). These authors suppose activity at involved chromosomal area, in this case of inhibitory character. According author's opinion, the number of double bonds of LCPUFA-OMEGA-3 has to be considered as much more important as compared with the number of carbon units.

DHA can also stimulate synthesis and production of adiponectin (Pérez-Matute et al., 2007) which correlates with former data on the decreased visceral obesity after diet supplementation with PUFA-OMEGA-3 (Hainer, 2004; Růžičková et al., 2004).

We found that authors of works about effect of DHA on gene expression (stimulating or inhibiting) did not presume to determine the location and mechanisms of this action. Their findings are based on mRNA measurement. Sufficient amount of analytic data for elucidation of coherent facts and for creation

of the final concept has not yet been published. So far, we can again state that up-to-date results show domination of processes having de facto protective or regenerative attributes.

Evolutional aspect and mutual ratio of unsaturated fatty acids groups and following consequence in sense of their functioning lead us to the following conclusions.

First of all, processes connected with immunity. Immunity itself represents very complicated group of mutually interconnected mechanisms defending and protecting the organism. Interpretation of immunity is unfortunately very often distorted by presentation of facts not taking history in consideration. The development of defence, protection of organism has its own history covering all from amoebic escape reaction, existence of protecting substances on body/mucosa surface, local unspecific mechanism, protective mimickers, anticipating locoreaction to phagocytosis, specific antibodies and memory register. Ultimatively – and this is very important – they regulate phase of immune reactions termination when defence mechanisms become redundant.

The effect of PUFA-OMEGA-6 and mainly the arachidonic acid and its metabolites can be explained that some of those molecules become part of organisms' immune system. Liberation of the arachidonic acid from plasmatic membrane by immune and not immunological stimuli leads to leucotrienes production. The effect of leucotrienes in specific area can be interpreted as a local defensive mechanism of unspecific character. Such processes have together with proinflammatory cytokines clear "defensive" character for specific noxae.

The liberalization of either DHA or EPA does not lead to such effect. First of all it represents a handicap for membrane ultrastructure and following functional defect. Diet supplement with DHA (EPA resp.) turns into beneficial and protective effects related to plasmatic membrane architecture renewal. This fact is linked to reparation of cell and tissue function. As one possible reason of beneficial effects of LCPUFA-OMEGA-3 on the state or prevention of obesity and insulin resistance, their evident anti-inflammatory acting is stressed (Kopecký et al., 2009).

The membrane damage can include the inner layer as well. In such case DHA (EPA) is released into cytoplasm. It is not clear yet, what happens then but we suppose that DHA molecule could play role in gene expression processes mentioned above. The idea of DHA molecule being coupled to some level or structure of reproductive process is recognized. There is also the possibility of meeting DHA molecule with small RNA fragments (cRNA) in cytoplasm (recent results suggest its importance in interaction between epigenetic factors and genome).

Thus, we can anticipate different effects and importance of DHA molecule depending in which compartment DHA was primarily released or transported into (including from unsaturated fatty acids pool). In the same time, we are aware of

the fact that DHA is a molecule of lipoid character and can therefore easily pass through plasmatic membrane.

Isolated DHA could represent a molecule with a new "role". Both its allocation into membrane structure and into genetic pathways can represent two mechanisms having similar effects: they represent an important part of the repair and renewal process following disintegration actions and signals. PUFA-OMEGA-6, mainly arachidonic acid, responds immediately to such signals with the release of its metabolites. Reparation and renewal processes follow with molecule of DHA as a participant and probably also as a trigger.

Considering all the complexity, we understand the role of both PUFA groups as a result of long evolution. At the same time we do not doubt any of other known roles and functions of PUFA in the mammalian organism.

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