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N-3 AND N-6 PUFAS IN HEALTHY AND DISEASED SKIN

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Summary

Western type diets do hardly provide the recommended intakes of certain long-chain polyunsaturated fatty acids (LC-PUFAs), although research revealed their functionality and essentiality that was even honored with a Nobel prize in 1982.
LC-PUFAs exert 2 major biological functions:
• **Structural elements of membranes**
A double layer of phospholipids, containing besides other FA also LC- PUFAs (arachidonic acid, docosahexaenoic acid), is responsible for the particular properties of membranes. They are highly selective permeability barriers that carry metabolic active proteins like the energy conversion process, gap junctions to control the flow of information between cells and receptors for external stimuli. The transdermal waterloss is mostly due to the linoleic acid content of the skin, although γ-linolenic acid might be as important as well.
• **Messengers**
All LC-PUFAs containing 20 carbon atoms are precursors of eicosanoids. This includes
• dihomo-γ-linolenic acid (DGLA): C20:3 ω-6
• Arachidonic acid (AA): C20:4 ω-6
• Eicosapentaenoic acid (EPA): C20:5 ω-3
Eicosanoids act as local hormones interfering with cellular regulation. In the skin, they can evoke pro-inflammatory or anti-inflammatory reactions, depending on the precursor fatty acid. A balanced application of ω-3 and ω-6 PUFAs, either by food or by supplements, may thus alleviate inflammatory skin disorders.
Based on these multiple involvements in our metabolism and their importance for health, the following recommendations have been elaborated by scientific societies and authorities:
Dnring a workshop on the essentiality of ω-6 and ω-3 fatty acids, April 7-9 1999, in Bethesda, a daily intake of about 0.65 g EPA plus DHA /day has been recommended. This is in good agreement with dietary guidelines, revision 2000, by the American Heart Association and with the qualified health claim issued by the FDA on October 31, 2000, and other scientific recommendations. Since this can hardly be achieved by eating fish only by a majority of the population, alternative sources have to be explored.

Riassunto

La cultura occidentale raccomanda con "poco calore" l'inserimento nella dieta di acidi grassi polinsaturi (LC-PUFAs) anche se gli studi ne hanno rivelato la funzionalità e la essenzialità, addirittura con un Nobel nel 1982.
Gli LC-PUFAs svolgono principalmente 2 funzioni biologiche come:
- Elementi strutturali delle membrane
Un doppio strato di fosfolipidi contenente oltre che altri acidi grassi anche LC-PUFA (acido arachidonico e docosaesanoico) è responsabile delle particolari proprietà delle membrane. Queste membrane sono barriere permeabili altamente selettive e necessarie per il trasporto di proteine metabolicamente attive e indispensabili per la conversione del processo energetico; fungono inoltre da messaggeri nel controllo del flusso delle informazioni tra le cellule e i recettori per gli stimoli esterni.
La perspiratio insensibilis è legata essenzialmente alla presenza nella pelle dell'acido linoleico, anche se svolge una funzione importante anche l'acido γ linolenico.
- Messaggeri
Tutti gli LC-PUFAs che contengono 20 atomi di carbonio sono precursori degli eicosanoidi come:
- l'acido diomo-γ-linolenico (DGLA) C20:3 ω-6
- l'acido arachidonico (AA) C20:4 ω-6
- l'acido eicosapentenoico (EPA) C20:5 ω-3

Gli eicosanoidi agiscono come ormoni locali che interferiscono con la regolazione della vita cellulare. Nella pelle possono indurre reazioni pro-infiammatorie o anti-infiammatorie in dipendenza del precursore dell'acido grasso.
Un'assunzione bilanciata di PUFAs ω-3 e ω-6, sia attraverso gli alimenti che attraverso dietetici, può alleviare eventuali processi infiammatori a carattere patologico.
La comunità scientifica e le autorità hanno perciò elaborato le seguenti raccomandazioni nell'uso dei PUFAs. Dati i loro molteplici coinvolgimenti nei nostri processi metabolici e visto il ruolo importante che rivestono per la salute, il 7-9 aprile del 1999 durante un meeting svoltosi a Betesda, è stata raccomandata l'assunzione giornaliera di circa 0,65g di EPA più DHA. Queste raccomandazioni sono in accordo con le linee guida alimentari consigliate sia nel 2000 dall'Associazione Americana per il Cuore che con quanto raccomandato dall'FDA il 31 ottobre, 2000.
Poiché per la maggior parte della popolazione risulta difficile mangiare più frequentemente la carne di pesce, ricca appunto di PUFAs, è necessario trovarne fonti alternative.

N-3 and n-6 PUFAs in healthy and diseased skin

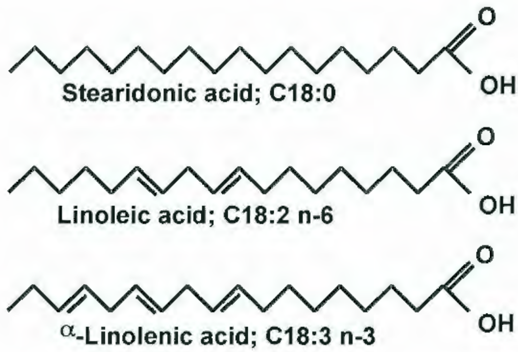
Good health depends on good nutrition. This simple relationship urged US authorities to establish the first recommendations for nutrients in 1943, which are currently being revised for the 11th time. Since their 1st publication, many nutrients have been identified to be critical for an adequate intake. To this list we have to add the long-chain polyunsaturated fatty acids (LC-PUFAs) because their availability in the food chain is limited. In order to bridge the gap between an inadequate intake and requirement, food items can been fortified or the deficiency can be bridged by supplements.

During the 50ies the essentiality of linoleic acid has been recognized since infants fed a linoleic acid deficient formula present a drying and flaking skin[1].

In 1989 only, the essentiality of ω-3 fatty acids has been discussed in the US, but no RDA has been issued due to lack of data[2]. Today, the requirement of α-linolenic acid (ω-3) as well as of linoleic acid (ω-6) is well accepted.

Both, linoleic acid (LA) and α-linolenic acid (ALA) must be elongated and desaturated; the former to dihomo-γ-linolenic acid (DGLA) and arachidonic acid (AA) and the latter to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) for full biological activities. Research during the past years revealed that the conversion of ALA to EPA and DHA is rather slow and insufficient in human beings. Therefore, several nutrition societies added EPA and DHA to the list of recommended nutrients taking into account that mankind should have access to these highly unsaturated fatty acids directly and not only via the precursor. Recent studies clearly show a health benefit from the intake of the highly unsaturated PUFAs γ-linolenic acid (GLA, 18:3 ω-6), eicosapentaenoic acid (EPA, 20:5 ω-3) and docosahexaenoic acid (DHA, 22:6 ω-3).

Fatty acids (FA) consist of a carbon chain of up to 24 atoms linked by single or double bonds and an acid group at the end. Double bonds occur either after the 3rd carbon atom leading to the ω-3 or n-3 FA, or after the 6th carbon atom (ω-6 or n-6 FA) (Fig.1). Animals and humans



lack the enzyme that is responsible to introduce the 2nd double bond at the correct position; therefore, for us, the precursor of all functional ω-6 FA, linoleic acid (18:2 ω-6) and the precursor of all functional ω-3 FA, α-linolenic acid (18:3 ω-3), are essential. Between two double bouds there are always two single bonds, which renders the PUFAs vulnerable against oxygen radicals. Furthermore, all double bonds are in the cis-configuration.

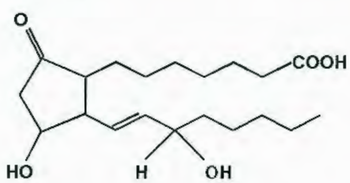
Thus, FA can be classified by following categories:

- Saturated (without double bonds)
- Unsaturated (with one or more double bonds)
- Monoenes (with one double bond) example: oleic acid in, e.g., in olive oil
- Polyenes (with two or more double bonds)
- ω-3 PUFA (1st double bond in position 3) example: EPA and DHA in fish oil
- ω-6 PUFA (1st double bond in position 6) example: γ-linolenic acid in borage oil and arachidonic acid in animal fat.

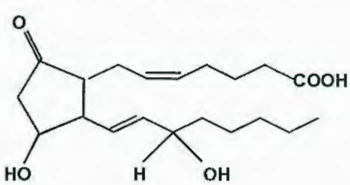
In a healthy diet all these categories have to be balanced against each other for a proper functioning of our metabolism.

Fatty acids exert 3 functions in the metabolism and its regulation:

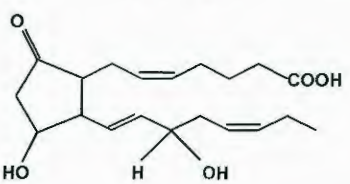
- **Source of energy:**
  Although this concerns mostly medium- and short chain saturated FA it is noteworthy that the FA are an excellent source of energy.
- **Structural elements of membranes**
  FA are the building elements for phospholipids that aggregate to a double layer to form the membranes. They are highly selective permeability barriers that carry other structural elements like proteins. These elements are responsible for metabolic activities like the energy conversion process, control of the information flow between cells, and they contain receptors for external stimuli. LC- PUFAs such as arachidonic acid docosahexaenoic acid gives them the particular physical property.
- **Messengers**
  All LC-PUFAs containing 20 carbon atoms are precursors of eicosanoids (Fig. 2). This includes



PGE$_1$
(ex DGLA)



PGE$_2$
(ex AA)



PGE$_3$
(ex EPA)

- dihomo-γ-linolenic acid (DGLA): C20:3 ω-6
- Arachidonic acid (AA): C20:4 ω-6
- Eicosapentaenoic acid (EPA): C20:5 ω-3

Cyclooxygenase and lipoxygenases convert these fatty acids into the corresponding prostaglandins, leukotrienes, thromboxanes, prostacylins and hydroxy-fatty acids.

Eicosanoids act as local hormones interfering with cellular regulation. They are involved in inflammation, regulation of blood flow, control of ion transport, modulation of synaptic transmission, termination of pregnancy, etc.

Prostaglandins and leukotrienes originating from DGLA or EPA are by far less active as pro-inflammatory agents than the corresponding derivatives of AA[3]. The intake of fish oil derived fatty acids leads to a decrease of AA in the membranes and, thus, to a lower production of the strongly pro-inflammatory eicosanoids, because the enzymes involved in the PUFA metabolism are the same[4].

The human epidermis has a limited capacity to metabolize fatty acids. It lacks the enzymes to introduce new double bonds, e.g. it cannot desaturate LA to GLA or DGLA to AA. However, the elongase is present, which converts GLA to DGLA[5]. This opens the unique opportunity to control the production of the pro-inflammatory eicosanoids by the supplementation of the competing fatty acids, GLA and EPA. Unfortunately, there is no direct source for DGLA, but GLA can be taken instead.

Furthermore, the epidermis expresses only the 15-lipoxygenase, but not the 5-lipoxygenase besides the cyclooxygenase. Therefore, the following set of eicosanoids can be produced by the epidermis:

- Out of arachidonic acid (20:4 w-6), which makes up 9 % of fatty acids in epidermal phospholipids:
  by the cyclooxygenase pathway: PGE$_2$, PGF$_{2\alpha}$, PGD$_2$;

by the 15-lipoxygenase pathway: 15-Hydroxyeicosatetraenoic acid (15-HETE)

- Out of LTA4 derived from stimulated leukocytes:
  by leukotriene A$_4$ hydrolase: LTB$_4$
- Out of dihomo-γ-linolenic acid (20:3 ω-6),

which is only a minor constituent of phospholipids:
by the cyclooxygenase pathway: PGE_1;
by the 15-lipoxygenase pathway: 15-Hydroxyeicosatrienoic acid (15-HETrE)

- Out of eicosapentaenoic acid (20:5 ω-3), which is not present in normal epidermis:
  by the 15-lipoxygenase pathway: 15-Hydroxyeicosapentaenoic acid (15-HEPE)
- Out of docosahexaenoic acid (22:6 ω-3), which is not present in normal epidermis:
  by the 15-lipoxygenase pathway: 17-Hydroxydocosahexaenoic acid (17-HoDHE)

15-Lipoxygenase products inhibit the formation of the chemotactic attractant LTB_4 in a dose dependent manner, the 15-HETrE being the most potent one. The 50 % inhibition of the 5-lipoxygenase occurs at 13 µmol/L 15-HETrE, 26 µmol/L 15-HEPE res. 17-HoDHE and at 40 µmol/L 15-HETE[6].

The significant interaction between the various sources of eicosanoids has been proven in numerous studies. Most of them have in common that AA derived eicosanoids have been counterbalanced by an other precursor given either as supplement or with food.

In a 120 day study 11 healthy men received a standard diet for 30 days followed by either 6 g DHA for the next 90 days (n=7) or LA (n=4). Both diets were supplemented by 20 mg α-tocopherylacetate to assure an adequate intake of vitamin E to protect the LC-PUFAs from oxidation. The DHA concentration in the phospholipids of peripheral blood mononuclear cells (PBMNC) increased from 2.3 wt% to 7.4 wt% in the verum group on the expense of AA that decreased from 19.8 wt% to 10.7 wt%. At the end of the study, lipopolysaccharide stimulation of PBMNC resulted in 60-75% lower release of prostaglandin E_2 and leukotriene B_4[7].

In order to test the health benefit of GLA, 160 patients suffering from atopic eczema received either 3 g borage oil (690 mg GLA) or a placebo for 24 weeks. The reduction of Costa score points was similar in both groups, although improvement of individual symptoms was observed in the verum group. An analysis of a subgroup taking into account the compliance of the patients showed that the volunteers of the verum group used significantly less diflucortolone-21-valerate cream than the participants of the placebo group[8]. This study underlines the usefulness of nutrients as a complementary measure during a normal, standard treatment.

These examples illustrate that membranes carrying mainly AA as LC-PUFA can only synthesize the strongly pro-inflammatory eicosanoids PGE_2, LTB_4 etc. Adding competitive precursor FA, GLA or EPA/DHA, results in a balanced reaction of the immune system.

CONCLUSION

The long-chain fatty acids arachidonic acid, dihomo-γ-linolenic acid and eicosapentaenoic acid are essential for the regulation of the immune system. γ-Linolenic acid can be elongated in the skin to DGLA and is, therefore, a suitable precursor. GLA as well as the fish oil fatty acids EPA/DHA are required for a balanced synthesis of eicosanoids and thus important for skin health. LC-PUFAs are useful for a complementary treatments, they do not replace medical measures. A balanced diet should contain ω-6 and ω-3 LC-PUFAs in a ratio of 5:1. Current recommendations for an intake of EPA/DHA vary between 0.65 g/d (ISSFAL)[9] and 1.1 g/d (BNF)[10]

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