Essential fatty acids, evening primrose oil, borage oil, rheumatoid arthritis, Raynaud phenomenon, Sjögren syndrome, dihomo-γ-linolenic acid

INTRODUCTION

Eicosanoid formation

The essential fatty acids (EFAs) have unique roles as precursor molecules of chemical regulators of inflammatory cell function (1). These regulators are the prostaglandins (PGs) and the leukotrienes (LTs), compounds synthesized and released by almost every tissue in the body and that participate in many biological functions, including the inflammatory and immune processes. The derivation of PGs and LTs from their percursor EFAs is illustrated in Figure 1. Dihomo-γ-linolenic acid (DGLA; 20:3n–6) leads to the formation of the 1-series PGs, arachidonic acid (20:4n–6) leads to the 2-series PGs, and eicosapentaenoic acid (20:5n–3) leads to the 3-series PGs. Most research centers on arachidonic acid, the precursor of the 2-series PGs and the 4-series LTs.

Altering the EFA content of the diet or administering different EFAs as supplements can modify the production of the various PGs and LTs. By altering the substrate EFA, for example, the ingestion of a diet rich in evening primrose oil (EPO) or borage oil (starflower oil) elevates DGLA concentrations, resulting in an increase in the 1-series PGs, eg PGE1 (2). In common with all PGs, PGE1 can induce the cardinal signs of inflammation: redness, edema, pain, heat, and loss of function. In contrast, however, the action of PGE1 on the inflammatory cells, ie, the polymorphonuclear leukocytes, is mostly inhibitory (3). PGE1 increases intracellular cyclic AMP (cAMP) and it is this increase in polymorphonuclear leukocyte cAMP that reduces the release of lysosomal enzymes, reduces polymorphonuclear leukocyte chemotaxis, and reduces the margination and adherence of leukocytes in the blood vessels. Similarly, the effect of PGE1 on lymphocytes is thought to be inhibitory (4). Exogenous addition of PGE1 inhibits both in vitro function of lymphocytes and in vivo responses mediated by lymphocytes. It has been suggested that PGE1 has a negative feedback role in chronic inflammation, initially aiding in the development of the cardinal signs of inflammation but later suppressing inflammation, and that this antiinflammatory effect might be useful in a disease characterized by inflammation such as rheumatoid arthritis.

A further benefit of a diet rich in compounds containing γ-linolenic acid (GLA; 18:3n–6), which is be metabolized to DGLA, is the inhibitory effect of GLA on LT synthesis. LTB4 is one of the major metabolic products of arachidonic acid metabolism and activates the leukocytes responsible for chemokinesis, chemotaxis, adherence, and granulation. Additionally, LTB4 enhances the presentation of C9b receptors. DGLA itself cannot be converted to LTs but can form a 15-hydroxyl derivative that blocks the transformation of arachidonic acid to LTs. An increase in the 1-series PGs, eg PGE1, may suppress inflammation through the metabolism of GLA to DGLA and thus competitive inhibition of the 2-series PGs and 4-series LTs. Much in vitro animal and human
work suggests that such a modification of PG and LT production does occur (2, 6, 7), as reviewed elsewhere in this supplement (8).

Membrane effects

Although the metabolism of various EFAs to PGs and LTs is important, one must remember that EFAs are key components of cell membranes and that altering the EFA profile may also modify inflammatory-cell behavior through membrane effects. For example, cell membrane flexibility is dependent on fatty acid content and an increase in the amount of saturated fatty acids within the macrophage membrane will reduce its endocytic activity (9).

Cell adhesion molecules

Leukocytes flow in the central area of the bloodstream. When activated, they migrate to the side of the blood vessel and then roll along the blood vessel until immobilized. After they are immobilized, the leukocytes pass through the endothelium into the tissue, where they can mediate the inflammatory response. The ability of polymorphonuclear leukocytes to roll on and adhere to the endothelium is mediated by various cell adhesion molecules. One of these cell adhesion molecules, E-selectin, is presented only on endothelial tissue. After the leukocyte migrates into the tissue, E-selectin is no longer required and is shed into the circulation. Interleukin 8 is responsible for leukocyte activation; thus, inhibition of its formation by GLA supplementation would also be expected to reduce polymorphonuclear leukocyte function. In a preliminary pilot study, we evaluated the effect of GLA on leukocyte aggregation in whole blood in response to N-formyl-methionyl, leucinyl, and phenylalanyl tripeptide and found that leukocyte aggregation was reduced after the 12-wk GLA treatment period (Figure 2, Table 1). A larger study is underway to investigate the effect of GLA supplementation on cell adhesion molecules.

Endothelial effects

Another potential mechanism whereby GLA and DGLA mediate their beneficial effects is through the fibrinolytic process. Fibrin is deposited in excess in rheumatoid joints and we have shown that the fibrinolytic process is inhibited in these
EFA treatment has been evaluated

Rheumatologic conditions in which EFA treatment has been evaluated

Raynaud phenomenon

Sjögren syndrome

Psoriatic arthritis

**Interest in treating psoriatic arthritis sufferers with GLA-rich supplementation developed following studies of this skin
In our own study (12), we excluded patients requiring second-line therapy, treated the patients for 12 mo (with a 3-mo placebo washout phase), and used liquid paraffin as the placebo. We showed a significantly lower requirement for nonsteroidal antiinflammatory drugs in subjects given 12 capsules EPO/d (540 mg GLA) and in those given an EPO–fish oil mix (450 mg GLA, 240 mg eicosapentaenoic acid) than in the placebo group (Table 1). Use of liquid paraffin as a placebo allowed us to attenuate what is normally a considerable placebo effect in this group of subjects. Unfortunately, with the higher doses of EFAs currently being studied (28), liquid paraffin is probably not an appropriate placebo.

The choice of an active placebo remains a problem. In our study of fish oil in rheumatoid arthritis (32), we used air-filled capsules as a placebo. At the end of the study, we contacted all patients by letter and only 1 of 30 placebo subjects had realized that the capsules were empty. Hence, air-filled capsules may be an appropriate choice for future studies. Other alternatives may include using the recently registered, nonabsorbable fat olestra, but this would not have the same energy value as the active treatment, or encapsulating the standard fat content of the diet in the country under study. The problem with the latter option is that it could increase saturated fat intake, which may be unethical (33).

Zurier et al (28) evaluated a high dose of GLA (2.8 g/d as the free fatty acid) against a placebo of sunflower seed oil. In this study, GLA treatment resulted in a statistically significant reduction in the signs and symptoms of rheumatoid arthritis disease activity. Fifty-six patients received a 6-mo course of either GLA or placebo followed by a single, blind, 6-mo study in which all patients received GLA. During the second 6 mo, disease activity improved in both groups. The GLA dosage used in this study was well tolerated. Further controlled studies of this dosage in rheumatoid arthritis are warranted.

CONCLUSIONS

Dietary manipulation of EFAs or supplementation with therapeutic doses of EFAs may be effective for treating inflammatory disorders (34, 35). The effects of n–6 EFAs have been poorly studied to date, however, and results are inconclusive for use of EFAs in the treatment of Raynaud phenomenon and Sjögren syndrome. More convincing evidence exists in support of EFAs use in rheumatoid arthritis; the study by Zurier et al (28) in which a high dose of GLA was evaluated is particularly interesting. It is possible that a new family of EFA antirheumatic drugs will soon be available. However, this is dependent solely on the completion of well-designed clinical studies that are double-blind, contain adequate power, and do not use an active placebo.

REFERENCES