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Essential fatty acids and inflammation

Essential fatty acids are 'essential' not only because of their physiological importance but because they must be derived in either direct or partially elaborated form from the diet. Thus these acids may be classified as vitamins (indeed they were once called vitamin F).

Two groups of fatty acids are essential to the body: the ω6 (n6) series, derived from linoleic acid (18:2 n-6) and the ω3 (n3) series, derived from α-linolenic acid (18:3 n-3). In these notations 18 is the number of carbon atoms in the molecule, the second number is the number of double carbon-carbon bonds (degree of unsaturation), and the number after the n denotes the position of the first double bond starting from the methyl (ω) end of the fatty acid chain. The figure shows the sequences of the two fatty acids. Fatty acids provide energy, are an integral part of cell membranes, and are precursors for prostaglandins, thromboxanes, and leukotrienes, collectively termed eicosanoids. Abundant experimental evidence supports the view that eicosanoids participate in development and regulation of immunological and inflammatory responses. Because most rheumatic diseases are characterised by inflammation, disordered immune regulation, and tissue injury there is much interest among rheumatologists in the role of eicosanoids in regulation of host defences. As the detrimental effects of therapy for the rheumatic diseases may be more difficult to manage than the diseases themselves there is a need for new, safe approaches to the treatment of these patients. Alteration of the eicosanoid profile by administration of fatty acid precursors other than arachidonic acid is one approach under investigation.

As eicosanoids derive from essential fatty acids, dietary manipulation or direct administration of precursor fatty acids has been used to alter the eicosanoid profile. Although changes in eicosanoid production owing to alteration of fatty acid intake form the basis of the current hypothesis for the anti-inflammatory effects of this type of treatment, it is likely that the precursor fatty acids themselves may alter immune responses. Animal and human studies have shown that changes in essential fatty acid intake alter the fatty acid composition of cell membranes. For example, in essential fatty acid deficiency, deprivation of linoleic acid leads to deficiency of arachidonic acid and impairment of prostaglandin synthesis. Essential fatty acid deficiency causes many pathological changes, but it also reduces the severity of inflammation in experimental animal models. Fasting also has a salutary effect on symptoms of patients with rheumatoid arthritis. As neither induction of essential fatty acid deficiency nor fasting are likely to be popular treatments it might be more prudent to modify or supplement, rather than delete, lipid intake.

The extraordinary rapidity with which platelets adhere to damaged tissue, aggregate, and release potent biologically active materials suggests that the platelet is well suited to be a cellular trigger for the inflammatory process. Thus efforts directed at suppression of thromboxane synthesis, enhancement of prostacyclin (prostaglandin I2) production, and inhibition of platelet aggregation may result in limitation of inflammatory responses. Fish oil lipids, rich in eicosapentaenoic acid (20:5 n3), inhibit formation of cyclo-oxygenase products (thromboxane A2, prostaglandin E2) derived from arachidonate. Newly formed thromboxane A2 has much less ability than thromboxane A2 to constrict vessels and aggregate platelets. In addition, production of prostaglandin I2 by endothelial cells is not reduced appreciably by increased eicosapentaenoic acid content, and the physiological activity of newly synthesised prostaglandin I2 is added to that of prostaglandin I2. Diets enriched in fish oil also reduce the amount of leukotriene B4 generated via the 5-lipoxygenase pathway in stimulated neutrophils and monocytes, suppress the chemotactic response of neutrophils to leukotriene B4, and reduce generation of platelet activating factor, interleukin 1, and tumour necrosis factor by stimulated monocytes. Fish oil supplements have therefore been used in attempts to suppress inflammation in experimental models and in patients with rheumatoid arthritis.8-10 Therapeutic benefits have been modest but encouraging. Evidence that fish oil administration enhances collagen induced arthritis in rats and exacerbates vasculitis in autoimmune mice11 dictates caution in the premature uncontrolled use of fish oil treatments in inflammatory diseases. Evidence obtained from experiments in vitro and in vivo in small animals and humans suggests that other novel fatty acids may be safe and effective anti-inflammatory and immunomodulatory agents. For example, certain botanical lipids, notably those extracted from seeds of the evening primrose and borage plants, contain relatively large amounts of γ-linolenic acid (18:3 n-6). This acid is converted rapidly to dihomo-γ-linolenic acid (20:3 n-6) the fatty acid precursor of the monoenic prostaglandins—for example, prostaglandin E1. In humans the 15 desaturase which converts dihomo-γ-linolenic acid to arachidonic acid is sluggish. Thus concentrations of arachidonate do not increase appreciably. Dihomo-γ-linolenic acid competes with arachidonate for oxidative enzymes, thereby reducing production of cyclo-oxygenase products derived from arachidonate. In addition, dihomo-γ-linolenic acid cannot be converted to inflammatory leukotrienes by 5-lipoxygenase. Instead, it is converted to 15-hydroxy-dihomo-γ-linolenic acid, which has the added ability of inhibiting 5-lipoxygenase activity.12 γ-Linolenic acid enrichment of diet suppresses acute and chronic inflammation as well as joint tissue injury in several experimental animal models.13 In animals treated with evening primrose or borage seed oils, cells from inflamma-
ory exudate are enriched in γ-linolenic acid and its elongated product dihomo-γ-linolenic acid. Exudate prostaglan-
din E2 and leukotriene B4 concentrations are reduced and 
leucocyte effector functions (chemotaxis, lysosomal 
enzyme release) are suppressed. Enrichment with dihomo-
γ-linolenic acid of synovial cells in culture leads to a marked 
reduction of prostaglandin E2 synthesis, a substantial 
increase in prostaglandin E1 production, and reduction in 
interleukin 1 induced synovial cell proliferation. Addition to 
cultures of arachidonic acid (which increases prostaglandin 
E2 substantially) or eicosapentaenoic acid does not modify 
synovial cell proliferation. The antiproliferative effect of 
dihomo-γ-linolenic acid is prevented by indomethacin.14 
Thus both marine and botanical lipids have anti-inflammatory 
actions owing to their ability to reduce synthesis of 
oxygenation products of arachidonic acid which are potent 
mediators of inflammation.

In addition to their role as eicosanoid precursors, fatty 
acids are of major importance in maintaining cell membrane 
structure and are key determinants of the behaviour of 
membrane bound enzymes and receptors.15 The fatty acid 
precursors can exert these functions directly and therefore 
may themselves be important regulators of immune 
responses. Dihomo-γ-linolenic acid suppresses interleukin 2 
production by human peripheral blood mononuclear cells 
in vitro, suppresses proliferation of interleukin 2 dependent 
human T lymphocytes, and reduces expression of activation 
markers on T lymphocytes directly, in a manner which is 
independent of conversion to prostaglandin.16 The observa-
tions indicate that fatty acids can modulate immune 
responses by acting directly on T cells and suggest that 
alteration of cellular fatty acids may be a worthwhile 
approach to control of inflammation.

Inflammation is central to the cutaneous manifestations of 
psoriasis and atopic eczema. In both conditions leukotriene 
B4 and 12-hydroxyeicosatetraenoic acid concentrations are 
increased in affected skin. Controlled trials, in which γ-
linolenic acid (in primrose seed oil) was used to treat atopic 
eczema, showed sufficient clinical benefit to warrant 
approval of such treatment by the National Health Service.17 
Administration of 1-1 g/day γ-linolenic acid to volunteers 
and patients with rheumatoid arthritis for 12 weeks (in an 
uncontrolled manner) resulted in enrichment of leucocytes 
with dihomo-γ-linolenic acid, significant reductions in 
meso-γ-prostaglandin E2 synthesis, and reduced synthesis of 
prostaglandins B2 and D6, and reduced synthesis in six of seven 
patients.18 Other studies have shown that γ-linolenic acid 
administration leads to increased prostaglandin E1 production 
by monocytes.19 A preliminary report20 indicating that 1-2 g γ-linolenic acid/ 
day given to normal volunteers for six weeks reduced 
interleukin 1 production by stimulated peripheral blood 
monocytes may also be relevant to its potential therapeutic 
effects. γ-Linolenic acid (540 mg/day in primrose seed oil) 
has been shown, in a 12 month long placebo controlled, 
double blind study to reduce pain and the need for non-
steroidal anti-inflammatory drugs in patients with rheuma-
toid arthritis.21 Lower doses of the acid (480 mg/day), used 
for shorter periods of time (12 weeks), were not useful 
treatment for patients with rheumatoid arthritis.22, 23 It may be 
of interest that in one of the negative studies22 the 
γ-linolenic acid supplement could be substituted for the 
non-steroidal anti-inflammatory drugs. Clearly, long term, 
multicentre, placebo controlled studies of a large number of 
patients are needed to determine whether any form of 
treatment is useful for patients with rheumatoid arthritis.

Few adverse effects of marine or botanical lipid adminis-
tration have been noted; stool softening and abdominal 
bloating have been reported. Nonetheless, potential adverse 
effects cannot be dismissed. Experience teaches that 
the longer a given treatment is used the greater the incidence of 
adverse effects. Administration of long chain poly-
unsaturated fatty acids increases the likelihood of lipid 
peroxidation with its associated toxic effects on cells. It is 
not known whether an increased requirement for an 
antioxidant (such as vitamins E and C) accompanies 
increased intake of long chain unsaturated fatty acids. 
Because these novel fatty acids can reduce inflammation and 
afflect monocytes the question arises as to whether they 
can compromise the immune system. Susceptibility to 
infection has not been seen as yet but must be considered.

The potential ability of particular fatty acids to regulate 
cell activation, immune responses, and inflammation is 
exciting to consider at the clinical, cellular, and molecular 
levels. A better understanding of how fatty acids modulate 
function of cells involved in host defence might lead to 
development of new, benign treatment for diseases charac-
terised by acute and chronic inflammation.