

Gamma Linolenic Acid: A Natural Anti-inflammatory Agent—Part I

by Rakesh Kapoor, Ph.D.

Gamma-linolenic acid, (GLA; cis-6, cis-9, cis-12-octadecatrienoic acid) is an *omega*-6 fatty acid that is naturally present in breast milk, beef, pork, chicken, and egg yolk. Over the past four decades, human and animal studies have confirmed anti-inflammatory properties of three commercialized sources of GLA: the oils of evening primrose (*Oenothera biennis*; 8 to 12% GLA), borage (*Borago officinalis*; 18 to 26% GLA), and black currant (*Ribes nigrum*; 13 to 17% GLA), for treating inflammatory conditions including arthritis and psoriasis; and for preventing diabetic neuropathy, high blood pressure, and skin disorders including itching, eczema, and dryness. During this same period, clinical trials have consistently found GLA to be a safe adjunct in the treatment of arthritis and several cancers. Although its exact mechanism of action is not well understood, GLA acts in several ways to exert its effects, including the modulation of eicosanoids (prostaglandins, leukotrienes) and cytokines, and by regulating genes that affect apoptosis and cell growth.

This two-part article reviews the current state of knowledge about the nutritional and health benefits of GLA.

GLA Metabolism

GLA is a functionally essential fatty acid (EFA) because it can correct the symptoms of EFA deficiency (1,2). It is produced endogenously in humans and animals as the first product of metabolism of linoleic acid (LA), an EFA of the *omega*-6 series. This reaction is catalyzed by the enzyme *delta*-6-desaturase (D6D) in what is the slowest and rate-limiting step in the metabolic pathway to GLA. Once synthesized, GLA is rapidly elongated to dihomogammalinolenic acid (DGLA) by the enzyme elongase (Fig. 1). Subsequently, DGLA is acetylated and incorporated into cell-membrane phospholipids. A small amount can be converted into arachidonic acid (AA) by the enzyme *delta*-5-desaturase (D5D).

The rate of formation of AA from DGLA is species- and tissue-specific. A rat metabolizes DGLA to AA in significant amounts, while humans and other species have limited capacity to form AA from DGLA. Cats are deficient in D6D and hence cannot synthesize GLA or the subsequent metabolites derived from LA (3), and must therefore eat a meat-based diet to obtain DGLA, AA, and other longer-chain metabolites of LA, such as DGLA and AA.

GLA in the Balance of Pro-Versus Anti-inflammatory Cytokines

DGLA competes with AA for cyclooxygenase (COX) and lipoxygenase (LOX) enzymes, and the metabolites of DGLA and AA that are produced by these two types of enzymes—the prostaglandins and leukotrienes, respectively—have actions that oppose each other (Fig. 1). In humans, the activity of D6D declines with age and in various diseases including arthritis, diabetes, hypertension, eczema, and psoriasis. In addition to this, lifestyle factors such as stress; smoking; excessive consumption of alcohol, of linoleic acid, and of saturated and trans-fatty acids; as well as nutritional deficiencies of vitamin B6, zinc, and magnesium inhibit D6D. For example, the populations of industrialized Western nations obtain substantial amounts of LA and AA from their meat-based diets that supply preformed AA, and by using vegetable oils rich in LA for cooking and in salad dressings.

The net result of all of the foregoing factors is diminished endogenous synthesis of GLA, with a functional deficit of DGLA that leads to an imbalance in prostaglandin/leukotriene production in which inflammatory prostaglandins derived from AA are produced in excess. Under such circumstances, supplementation with GLA restores balance to the system of inflammatory versus anti-inflammatory cytokines, and may explain why such supplementation has been found beneficial in these populations.

Anti-inflammatory and Immunomodulatory Activities of GLA

Uncontrolled inflammation damages healthy cells and has been implicated in many diseases including cancer, cardiovascular disease, diabetes, Alzheimer's disease, cystic fibrosis, multiple sclerosis, ulcerative colitis, inflammatory bowel disease, and autoimmune diseases including arthritis and psoriasis.

Cells of the immune system, including polymorphonuclear leukocytes (PMNs), monocytes, splenocytes, Kupffer cells, macrophages, and natural killer (NK) cells, take up GLA and rapidly elongate it to DGLA, which is then incorporated into phospholipids in these cells' membranes. Following an inflammatory stimulus, the enzyme phospholipase A2 (PLA2) releases DGLA from the cells' membranes, and this released DGLA competes with AA for metabolism by COX and LOX enzymes. Metabolism of DGLA by COX enzymes produces both thromboxane A1 (TXA1) and PGE1, whose chief effects are anti-inflammatory and vasodilatory(4); the metabolism of DGLA by 15-LOX generates 15-hydroxyeicosatrienoic acid (15-HETE), which inhibits the enzyme 5-LOX, thereby inhibiting the production of leukotriene B4 (LTB4) by neutrophils (Fig. 1) (5, 6).

This inhibition is beneficial because LTB4 amplifies the inflammatory response: it is a very potent chemotactic factor that attracts neutrophils to sites of inflammation; increases the adherence of leukocytes to endothelial cells; enhances the migration of T-lymphocytes in vitro, stimulates the release of interferon gamma (IFN-g) and production of interleukin-2 (IL-2) by T-cells, and promotes the biosynthesis of IL-1 by monocytes, all of which amplify the inflammatory response. IL-2 is a proinflammatory cytokine that stimulates the production and induction of T-lymphocytes (including lymphokine activated T-lymphocytes and natural killer cells). It also stimulates the production of various cytokines including IL-1, tumor necrosis factor and IFN-g, whereby it amplifies the proinflammatory actions.

Several studies have shown the inhibition by GLA of LTB4 production by stimulated neutrophils.(7-9). The in-vitro inhibitory concentration of 15-HETE for 5-LOX was observed to be 5 mM (10).

Besides exerting an anti-inflammatory effect by inhibiting COX and LOX pathways that generate mediators of inflammation, GLA also counteracts inflammation by affecting pathways of cytokine synthesis. For example, it has been shown to dose-dependently inhibit the mitogen-induced production by human peripheral blood mononuclear cells (PBMCs) of IL-2 (11)—an effect that appeared to be independent of the COX system, since indomethacin, a COX inhibitor, failed to suppress such synthesis of IL-2.(11) Besides this, DGLA was shown to inhibit the IL-2-dependent proliferation of T-lymphocytes isolated from the synovial tissue and synovial fluid of arthritis patients (13). It is possible that the observed GLA- and DGLA-mediated inhibition of IL-2 results from an effect of these fatty acids on early-response genes, since GLA has been shown to reduce an increase in expression of the c-fos oncogene and decrease in expression of the c-myc oncogene in T-cells (12).

A further finding with DGLA, and also with GLA, although less potently, was that both of these fatty acids inhibited the IL-1-induced proliferation of T lymphocytes.(14) This inhibition did not occur through any action of DGLA or GLA on a prostaglandin-synthetic pathway, since COX inhibitors failed to affect the two fatty acids' counterproliferative effect on the T lymphocytes (14). GLA has also been found to inhibit the release of IL-1 from LPS-stimulated monocytes without affecting the basal release of this cytokine, suggesting that it may work to inhibit inflammation by limiting the excessive release of IL-1b without interfering with its necessary host-defensive functions (15). IL-1 β has many actions in the body and is mainly a pyrogenic (fever inducing) cytokine. It plays a major role in acute phase response. It can increase the pain sensitivity of uninjured tissues in proximity to the injury that may be mediated via an increase in excitability of neurons through induction of COX-2 in central nervous system, leading to increased production of PGE2 . (Samad, T. A.; Moore, K. A.; Saperstein, A.; Billet, S.; Allchorne, A.; Poole, S.; Bonventre, J. V.; Woolf, C. J. : Interleukin-1-beta-mediated induction of Cox-2 in the CNS contributes to inflammatory pain hypersensitivity. *Nature* 410: 471-475, 2001). It also plays an important role in cancer invasiveness and metastasis (Voronov, E.; Shouval, D. S.; Krelin, Y.; Cagnano, E.; Benharroch, D.; Iwakura, Y.; Dinarello, C. A.; Apte, R. N. : IL-1 is required for tumor invasiveness and angiogenesis. *Proc. Nat. Acad. Sci.* 100: 2645-2650, 2003.)

Thus, GLA-rich oils have the potential to favorably modulate immune function and the inflammatory response against arthritis and other autoimmune diseases.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an autoimmune disease associated with the destruction of cartilage and inflammation of joints. There is no cure for RA; although its progression may be slowed by disease-modifying antirheumatic drugs (DMARDs) and monoclonal antibodies, its treatment is still largely symptomatic involving steroids and nonsteroidal anti-inflammatory drugs, and in many cases joint-replacement surgery is ultimately needed. GLA has been shown to exert anti-inflammatory and immunomodulatory effects both in laboratory animal models of RA and in humans with the disease. In clinical trials, GLA derived from borage oil, given at an oral dosage of 1.4 g/day (16) or 2.8 g/day of GLA (17) for a period of 6 months, significantly reduced morning stiffness, swollen-joint counts and scores, tender-joint counts and scores, and platelet counts. The only side effects of GLA were belching, flatulence, and soft stools. In another study, doses of 540 mg/day of GLA or 450 mg/day of GLA accompanied by 240 mg/day of eicosapentaenoic acid (EPA) given for 12 months significantly reduced the need for NSAIDs (18). Yet at 3 months after the conclusion of treatment with GLA, all of the patients in this study needed a full dose of NSAIDs, indicating that GLA and/or EPA had NSAID-sparing effects. In an open-label study, 1.1 g/day of GLA given for 12 weeks reduced inflammation in arthritic patients and also reduced the release of PGE₂, LTB₄, and LTC₄ (19).

A recent review of the literature on alternative and complementary therapies found strong support for GLA in the treatment of RA (20), and a meta-analysis of published studies of GLA concluded that in addition to having an NSAID-sparing effect, it is beneficial in reducing morning stiffness, by a duration of approximately 73 minutes (21). However, the dosage of GLA required for the treatment of arthritis is not well established, and in various studies has ranged from 340 mg/day to 2.8 g/day. Moreover, clinical trials of GLA at dosages below 500 mg/day and for periods of less than 6 months have generally failed to show beneficial effects (22,23).

Atopic Dermatitis

Patients with atopic dermatitis have been found to have higher than normal concentrations of LA and lower concentrations of GLA, DGLA, and AA in their plasma phospholipids (24), suggesting a defect in the D6D metabolism of LA. Their failure to show a flushing response to topically applied niacin suggesting that patients with atopic dermatitis also have defects in their prostaglandin-synthetic pathways that prevent the synthesis of vasodilatory prostaglandins. Other studies have shown subnormal levels of DGLA in the breast milk of atopic mothers (25,26), rendering their breast-fed infants prone to dermatitis.

These observations suggest that dietary GLA or DGLA should help prevent or treat atopic dermatitis, or both. This was indeed the case in a double-blind, placebo-controlled trial of evening primrose oil given to 60 adults and 39 children with moderate to severe atopic dermatitis (27). In this trial the adult patients received either 4, 8, or 12 capsules daily of GLA at 45 mg per capsule, while the children were given 2 or 4 capsules daily. The respective placebo groups received capsules containing liquid paraffin. Treatment for all groups continued for 12 weeks. The lower dose of GLA [4 capsules in adults and 2 capsules in children] provided relief only from itching while the higher doses of GLA provided significant relief from itch, scaling and overall impression of severity as assessed both by a physician and by the patient (27). The children in the study did not have as good results as the adults, probably due to lower dose of GLA or a greater placebo response.

Another study in which GLA was given at a dosage of 3.0 g/day for 28 days to children with atopic dermatitis, found a significant reduction in both itching and the use of antihistamines, without any treatment-related side effects (28). Although no complete remission of disease was seen in any of the children in this study, gradual improvements were observed in erythema, excoriations, and lichenification. On the other hand, a double-blind crossover study of borage oil versus corn oil for atopic eczema in 3- to 17-year-old patients, reported no beneficial effects of borage oil treatment (29).

Eczema

In a double-blind, placebo-controlled multicenter trial involving 160 patients with atopic dermatitis and moderate eczema, reflected by a Costa score of 20 to 36 points, (31) 24 weeks of treatment with borage oil at 3.0 g/day—providing 690 mg GLA daily—produced no significant benefit as compared to the placebo of migliol, an oil without GLA, when all patients, including those who did not follow the study protocol, were included in the data analysis. However, when the subgroup of patients who did not follow the study protocol was excluded from analysis, borage oil was found to have significantly reduced the use of the steroid cream that was allowed to patients as a treatment option in the study (31). Moreover, another double-blind study (32) that reported no beneficial effect on atopic eczema of a 12-week course of 920 mg/day of GLA from borage oil in adults and half this dose in children had several major limitations, including data analysis for only 140 of the 151 patients recruited into the study, and noncompliance with the study protocol, which is the single most important reason for failure of treatment in dermatologic practice (33).

Borage oil, through its content of LA, also appears to reduce the high transepidermal water loss from eczematous as compared to normal skin. When applied topically to infants (30) with seborrheic dermatitis, borage oil increased their serum LA content—suggesting the transdermal absorption of LA, normalized their transepidermal water loss, and relieved the symptoms of dermatitis within 3 to 4 weeks (30).

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