Gamma Linolenic Acid: An Antiinflammatory Omega-6 Fatty Acid

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Abstract: Inflammation plays an important role in health and disease. Most of the chronic diseases of modern society, including cancer, diabetes, heart disease, arthritis, Alzheimer's disease, etc. have inflammatory component. At the same time, the link between diet and disease is also being recognized. Amongst dietary constituents, fat has gained most recognition in affecting health. Saturated and trans fatty acids have been implicated in obesity, heart disease, diabetes and cancer while polyunsaturated fatty acids (PUFAs) generally have a positive effect on health. The PUFAs of omega-3 and omega-6 series play a significant role in health and disease by generating potent modulatory molecules for inflammatory responses, including eicosanoids (prostaglandins, and leukotrienes), and cytokines (interleukins) and affecting the gene expression of various bioactive molecules. Gamma linolenic acid (GLA, all cis 6, 9, 12-Octadecatrienoic acid, C18:3, n-6), is produced in the body from linoleic acid (all cis 6,9-octadecadienoic acid), an essential fatty acid of omega-6 series by the enzyme delta-6-desaturase. Preformed GLA is present in trace amounts in green leafy vegetables and in nuts. The most significant source of GLA for infants is breast milk. GLA is further metabolized to dihomogamma linlenic acid (DGLA) which undergoes oxidative metabolism by cyclooxygenases and lipoxygenases to produce anti-inflammatory eicosanoids (prostaglandins of series 1 and leukotrienes of series 3). GLA and its metabolites also affect expression of various genes where by regulating the levels of gene products including matrix proteins. These gene products play a significant role in immune functions and also in cell death (apoptosis). The present review will emphasize the role of GLA in modulating inflammatory response, and hence its potential applications as an anti-inflammatory nutrient or adjuvant.

INTRODUCTION

Inflammatory response is a friend and a foe. Acute inflammatory response is essential for survival of host as it plays an important role in host defense mechanisms (in killing of invading microorganisms, damaged cells, wound healing, tissue repair, etc.). Chronic/uncontrolled inflammatory response, on the other hand, leads to self tissue damage, causing chronic diseases like arthritis, psoriasis, etc. Research in last five decades has confirmed involvement of inflammation in various chronic diseases like heart disease, cancer, diabetes, Alzheimer's disease, parkinsonism, multiple sclerosis, and lupus nephritis, etc. [1-6]. The cause-effect relationship of inflammation in these diseases is not established yet. Of these, heart disease, cancer and diabetes are major diseases of industrialized world that account for over 50% of death from all causes.

In recent years, the understanding of role of diet in health and disease is being advanced at a rapid rate. Epidemiological studies have linked the diet with various chronic diseases (heart disease, diabetes, cancer, metabolic syndrome, etc.). Diets can modulate the inflammatory processes and also affect the gene expression in the body and hence, are linked to various disease incidences. The proper diet can therefore, play a significant role in prevention of disease and hence, maintenance of good health. Of many dietary constituents, fat has gained most importance in affecting health. Fatty acids play an important role in mediation of inflammatory responses, in addition to being a energy dense nutrient and a carrier of fat soluble vitamins.

The present review outlines the status of our current understanding on gamma linolenic acid in health and disease and its applications in prevention and treatment of diseases and to improve the efficacy of therapeutic agents.

GAMMA LINOLENIC ACID (GLA)

GLA (cis 6, cis 9, cis 12-Octadecatrienoic acid) is produced in the body as an intermediate in the metabolism of linoleic acid (LA), an essential fatty acid of omega-6 series by the action of enzyme delta-6-desaturase. This reaction is very slow and is further restricted during nutritional deficiencies of vitamins, minerals (zinc, cobalt, etc.), and also during inflammatory conditions like arthritis, psoriasis. Hypertension, diabetes, and several other diseases also impair the activity of this enzyme, leading to insufficient production of GLA in the body. Life style factors like stress, smoking, and alcohol, saturated and trans fats and preformed arachidonic acid and eicosapentaenoic acid also inhibit the enzyme. Once formed or administered, GLA is rapidly elongated to dihomogamma linolenic acid (DGLA) which is incorporated into the cell membrane phospholipids following acylation reaction catalyzed by acyl transferases. DGLA is the active form produced from GLA that mediates most of the physiological actions of GLA. A small amount of DGLA

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can also be converted to arachidonic acid (AA) by the enzyme delta-5-desaturase. However, this reaction is slow and the extent of formation of AA from DGLA is dependent on the dietary and environmental factors. Preformed AA (from meat and dairy) [7], eicosapentaenoic acid (EPA, from fish) [8], and sesamin [9] (from sesame seeds) inhibit the enzyme and thereby prevent formation of AA.

Membrane bound DGLA is released by the action of enzyme phopholipase A_2 (PL A_2). Once released, it is competes with AA for enzymes cyclooxygenases (COX) and lipoxygenases (LOX) to produce short lived second messengers that are responsible for cell – cell communications and mediation of physiological effects of these fatty acids. The cyclooxygenase products of DGLA include prostaglandins of series 1 (PGE_1) and thromboxane A_1 (TxA_1). These products of COX action exert anti-inflammatory, vasodilatory and anti-aggregatory actions. DGLA produces 15-hydroxyeicosatrienoic acid (15-HETrE) by the action of 15-LOX. 15-HETrE is a strong inhibitor of 5-lipoxygenase, whereby it inhibits production of leukotriene B_4 (LTB_4) from inflammatory cells including neutrophils [10,11]

GLA has gained importance in last four decades for its anti-inflammatory [12-16] and anti-cancer [17-22] actions. It also improves nerve conduction velocity in diabetic patients [23,24], leading to improved blood flow and reduced tingling of extremities. Due to these actions of GLA, many sources of GLA have been commercialized.

The significant commercial sources of GLA include the oils of, borage (*Borage officinalis*, 20 – 26% GLA), black current (*Ribes nigrum*, 15-18%) and evening primrose (*Oenoethera biennis L*, 8 – 12% GLA). The other sources include echium (Echium plantagineum), hemp (*Cannabis sativa*), fungus (Mortierella isabellina, Mucor fragilis).

GLA AS AN ANTIINFLAMMATORY NUTRIENT

GLA and Inflammation

GLA exerts antiinflammatory activity through formation of DGLA. DGLA is a substrate for COX and LOX enzymes. As discussed above, both COX and LOX products of DGLA exert anti-inflammatory activities. These actions may help in prevention/treatment of inflammation induced diseases including rheumatoid arthritis, psoriasis, atopic dermatitis, etc. In rheumatoid arthritis patients, GLA alone is not sufficiently potent to relieve pain and inflammation acutely. It requires a longer period of administration for a clinical response [7,25,26]. Several clinical trials have confirmed that GLA reduces inflammation, tender joint scores, morning stiffess [14,15,26-28] and reduces the requirement for NSAIDs [27]. When combined with anti-inflammatory drugs, it supplements the anti-inflammatory actions of drugs. Due to this reason, it is also called as Non-steroidal anti-inflammatory drugs (NSAID) sparing fatty acid in arthritic patients [27]. NSAIDs inhibit the COX enzyme non-selectively, whereby, they also prevent the formation of anti-inflammatory and vasodilatory PGE1. Due to inhibition of COX enzymes, NSAIDs stimulate the production of LOX products from arachidonic acid (AA) [29,30] which cause vasoconstriction. Due to reduced production of PGE1 and increased production of LOX products in patients taking NSAIDs chronically, gastric mucosa may suffer ischemic insult due to reduced blood supply. This may be responsible for gastric side effects of NSAIDs like gastric ulcers, and perforation [30,31]. On the other hand, DGLA acts as a synergistic molecule with NSAIDs by producing anti-inflammatory prostaglandins and leukotrienes. By inhibiting the production of LTB4, and stimulating the production of PGE1, DGLA maintains the normal circulation to gastric mucosa, preventing the gastric side effects of NSAIDs [32].

In Sjogren's syndrome patients, oral administration of GLA was shown to reduce ocular discomfort by reducing the inflammation and increasing the tear content of PGE1 [33] and in patients suffering from acute lung injury, GLA in combination with EPA improved gaseous exchange [34]. In a model of multiple trauma, parenteral administration of GLA was shown to increase survival [35] . Topically applied GLA was shown to relieve symptoms of uremic pruiritis [36], a common problem in hemodialysis patients.

GLA and Cancer

Cancer represents the second leading cause of death in industrialized countries. Anticancer drugs show significant toxicity as these drugs are non-selective in exerting toxic effects on cancerous and normal cells. GLA has been shown to exert tumoricidal activity against a variety of cancers including cancers of breast, pancreas, colon, brain, etc. [17,21,22,37,38]. GLA also inhibits metastasis of cancer cells [22,39-41]. The inhibition of metastasis is mediated through a combination of mechanisms. GLA has been reported to inhibit excessive expression of osteonectin (or SPARC), a protein involved in cancer cell migration [22] while it stimulates expression of metastasis suppressor genes that produce proteins that are involved in suppression of metastasis [39]. The anticancer actions of GLA are mediated through direct cytotoxic action of GLA on cancer cells [21], inhibition of angiogenesis in tumor cells [42], stimulation of apoptotic cell death [43] and gene activation and also through conversion to eicosanoids *via* DGLA. Studies have shown that when combined with anticancer agents, GLA not only improved the efficacy of anticancer drug, but also reduced the side effects. In in-vitro studies, GLA has been shown to improve the efficacy of anticancer drugs like paclitaxel, vinorelbine, doxorubicin, epirubicin, mitoxantrone and idarubicin, 5-fluorouracil, and germcitabine [44-47]. These actions are mediated through several mechanisms including down regulation of estrogen receptors [20,48], inhibition of 5α-reductase enzyme, inhibition of cell adhesion molecules like vCAM, ICAM, E-selectin, and urokinase type plasminogen activator, etc. Clinical trial in breast cancer patients has confirmed that when given in combination with tamoxifen, GLA improved the efficacy of tamoxifen, reduced the side effects and time to response to therapy [20]. GLA has been shown to improve the transcutaneous absorption of tamoxifen [49,50]. This strategy can be employed for local delivery of tamoxifen to the cancerous breast tissue and hence avoiding the side effects of the drug. GLA in itself being a tumoricidal compound will synergistically act with tamoxifen.

In one study, lithium salt of GLA was conjugated to iodized lymphographic oil (LGIOC) and injected intra-arteri-

ally at a site close to the tumor feeding vessel in 4 patients suffering from stage 4 cancers [38]. Of these patients, 2 were suffering from hepatocellular carcinoma, one giant cell tumor of the bone, and one with renal cell carcinoma. The injection of GLA derivative caused permanent occlusion of blood vessel feeding to the tumor, resulting in reduction in the size of tumor. The treatment was well tolerated. In another study, when GLA was injected into tumor cells in patients suffering from advanced glioma, it caused significant reduction in tumor mass, and improved the survival in these patients over 2 years [51].

INSULIN RESISTANCE AND DIABETES

Insulin resistance is a major problem as it occurs before clinical onset of diabetes. Insulin resistance also plays a significant role in metabolic syndrome. The exact cause of insulin resistnace development is not well understood. Several drugs have been known to cause impairment of insulin action. Glucocorticoids, in particular cause insulin resistance and can also show the cardiac side effects. It was shown that dexamethasone induced insulin resistance was associated with reduced cardiac DGLA levels and increase AA levels [52]. These changes in cardiac fatty acids may contribute to cardiac side effects of glucocorticoids. A recent analysis of plasma of diabetic children during and after diabetic ketoacidosis revealed that GLA levels were lower during ketoacidosis but were brought to normal levels following successful treatment [53]. The earlier studies have shown that treatment with GLA improves the nerve conduction velocity in diabetic patients and animals. These data suggest that GLA can be an important nutrient and also as adjuvant in the prevention of complications of diabetes.

SUMMARY

The above discussion highlights the physiological and pharmacological roles of GLA in regulating inflammatory responses. The data presented above suggest that GLA can be effectively used in combination with various pharmaceutical agents to improve the efficacy of these drugs and also to reduce the side effects, which is a serious concern affecting the quality of life of the patients. GLA can be used as a carrier for these medicines or can be co-administered.

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