Reducing Pain and Inflammation Naturally. Part II: New Insights into Fatty Acid Supplementation and Its Effect on Eicosanoid Production and Genetic Expression

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Abstract: Doctors and patients can achieve significant success in the treatment of pain and inflammation by using dietary modification along with nutritional, botanical, and fatty acid supplementation. The first article in this series reviewed recent diet research and the basic biochemistry of fatty acid metabolism, and this second article will provide doctors with a profound understanding of the importance of optimal fatty acid supplementation and will review the clinical benefits of this essential therapy. This review contains the most concise, detailed, up-to-date, and clinically relevant description of fatty acid metabolism that has ever been published in a single article.

INTRODUCTION

Chiropractic and naturopathic physicians are the only doctorate-level healthcare providers with graduate-level training in therapeutic nutrition and are emerging as the leaders in the treatment and prevention of long-term health disorders, including nearly all of the chronic diseases seen in clinical practice such as obesity, hypertension, adult-onset diabetes, hypercholesterolemia, allergies, asthma, arthritis, depression and a long list of other musculoskeletal and non-musculoskeletal conditions.[1,2] With the increasing substantiation of the effectiveness and cost-effectiveness of the nutritional management of these problems, and the documentation of the excessive cost and adverse effects generally associated with pharmaceutical medications, we are approaching a paradigm shift in healthcare which will eventually (re)position the practitioners of holistic natural healthcare in their proper place—at the forefront of patient management.

Healthcare providers of all disciplines are obligated to act responsibly to protect the health of the public. Current research published in peer-reviewed medical journals suggests that over-utilization of allopathic medical care endangers patients' health by exposing patients to prescribing errors[3], hospital injuries, and what is described as "substandard care."[4] A recent article in the *New England Journal of Medicine*[5] concluded that deficits in allopathic medical care pose "serious threats to the health of the American public." A 1997 review published by the American Academy of Family Physicians[6] stated, "Recent estimates suggest that each year more than 1 million patients are injured while in the hospital and approximately 180,000 die because of these injuries. Furthermore, drug-related morbidity and mortality are common and are estimated to cost more than $136 billion a year." New research also shows that several popular "antidepressant" drugs actually increase the risk for suicide in children[7] and adults[8,9,] and, similarly, "antipsychotic" drugs may worsen clinical outcomes in a large percentage of patients with mental illness.[10] Chiropractic diet therapy—not drugs—is the most effective treatment for chronic hypertension.[11, 12] Many anti-inflammatory drugs for the treatment of joint pain actually promote joint destruction[13, 14, 15] and the newer selective cyclooxygenase inhibitors carry an unjustifiable cost[16, 17] and fail to deliver improved efficacy[18] despite significantly increasing the risk for kidney damage, hypertension, myocardial infarction, stroke, and sudden death.[19, 20, 21] On the other hand, natural treatments such as dietary improvements and fatty acid supplementation have been shown to safely reduce the need for medical treatments, to improve health, to alleviate many common diseases, and to prolong life at lower cost, negligible risk, and with improved overall outcomes.[22, 23] **In order to reduce costs, promote health, and reduce iatrogenic disease, our healthcare paradigm must change from "disease treatment with drugs and surgery" to "health promotion with therapeutic nutrition and lifestyle improvements."** It is safe and reasonable to predict that in the near future, customized dietary improvement, therapeutic nutrition, lifestyle modification, and fatty acid supplementation will be viewed as integral components of patient care for all patients with all diseases. Doctors must therefore be informed of new research on how to use these interventions skillfully.

The combination of dietary improvement and skillful nutritional intervention as reviewed by the current author in the first article in this series[24] and in greater detail elsewhere[25] is the single most powerful approach for the effective treatment of a wide range of conditions. Following closely behind general dietary modification, fatty acid supplementation offers clinicians the opportunity to improve the health of their patients in ways that no other single treatment can.

FATTY ACID SUPPLEMENTATION: UNDERSTANDING IS THE KEY TO MASTERY

An accurate and detailed understanding of fatty acid metabolism is important for the complete and effective management of many clinical conditions including mental depression, coronary artery disease, hypertension, diabetes, other inflammatory/autoimmune disorders, and many of the musculoskeletal conditions encountered in clinical practice. The practical application of this information is

relatively straightforward, and with a detailed understanding of precursors and modulators of fatty acid, prostaglandin, and leukotriene metabolism, clinicians can facilitate or restrict the production of bioactive chemicals to promote the desired clinical result. The basics of fatty acid metabolism were reviewed previously; here we focus on clinical applications. We will focus on the fatty acids with the greatest promise for clinical benefit: alpha-linolenic acid, gamma-linolenic acid, eicosapentaenoic acid, docosahexaenoic acid, and oleic acid. Biochemical pathways and clinical implications of fatty acid metabolism are detailed in Figures 1 and 2.

Figure 1. Metabolism of omega-3 fatty acids and related eicosanoids

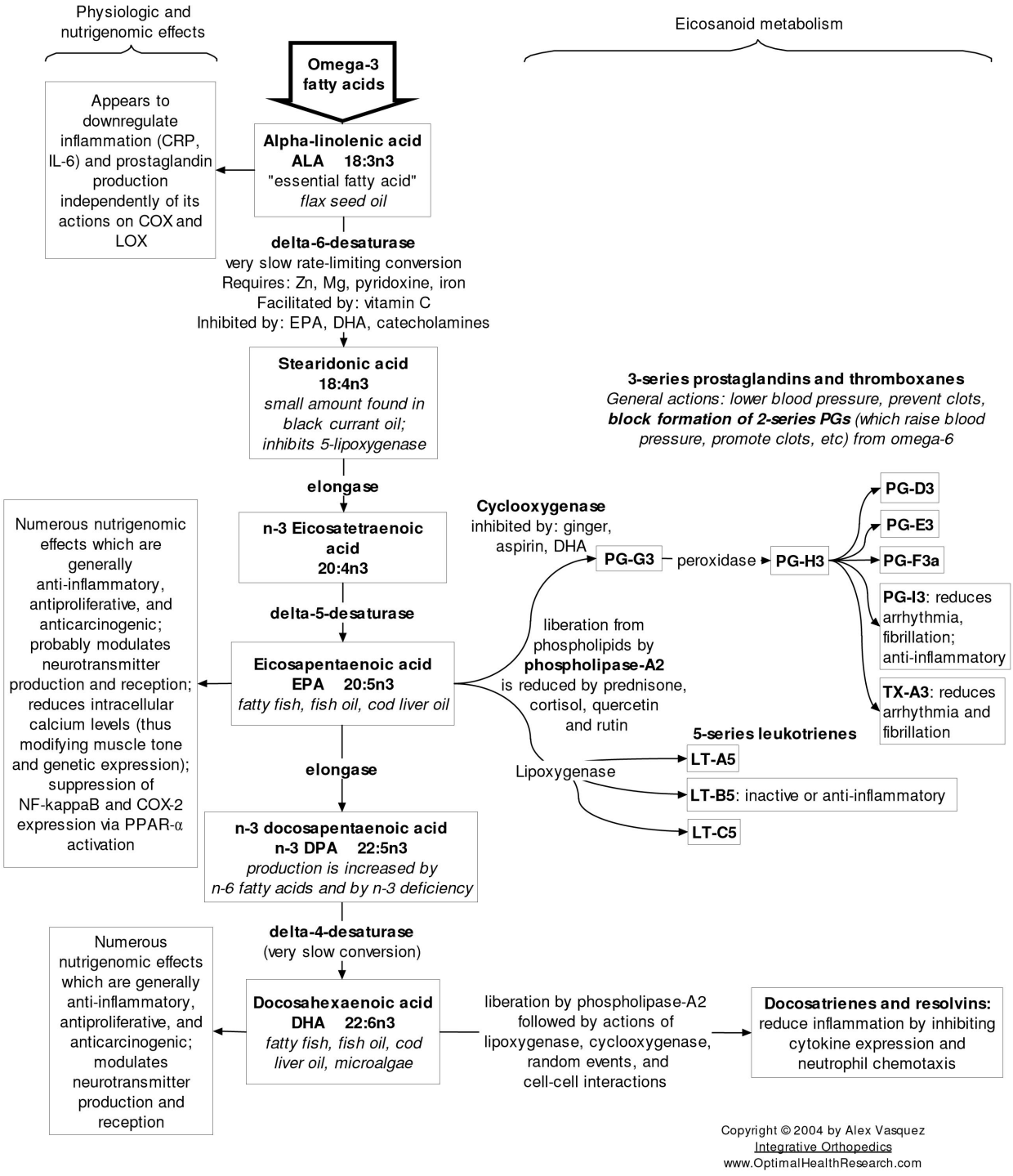
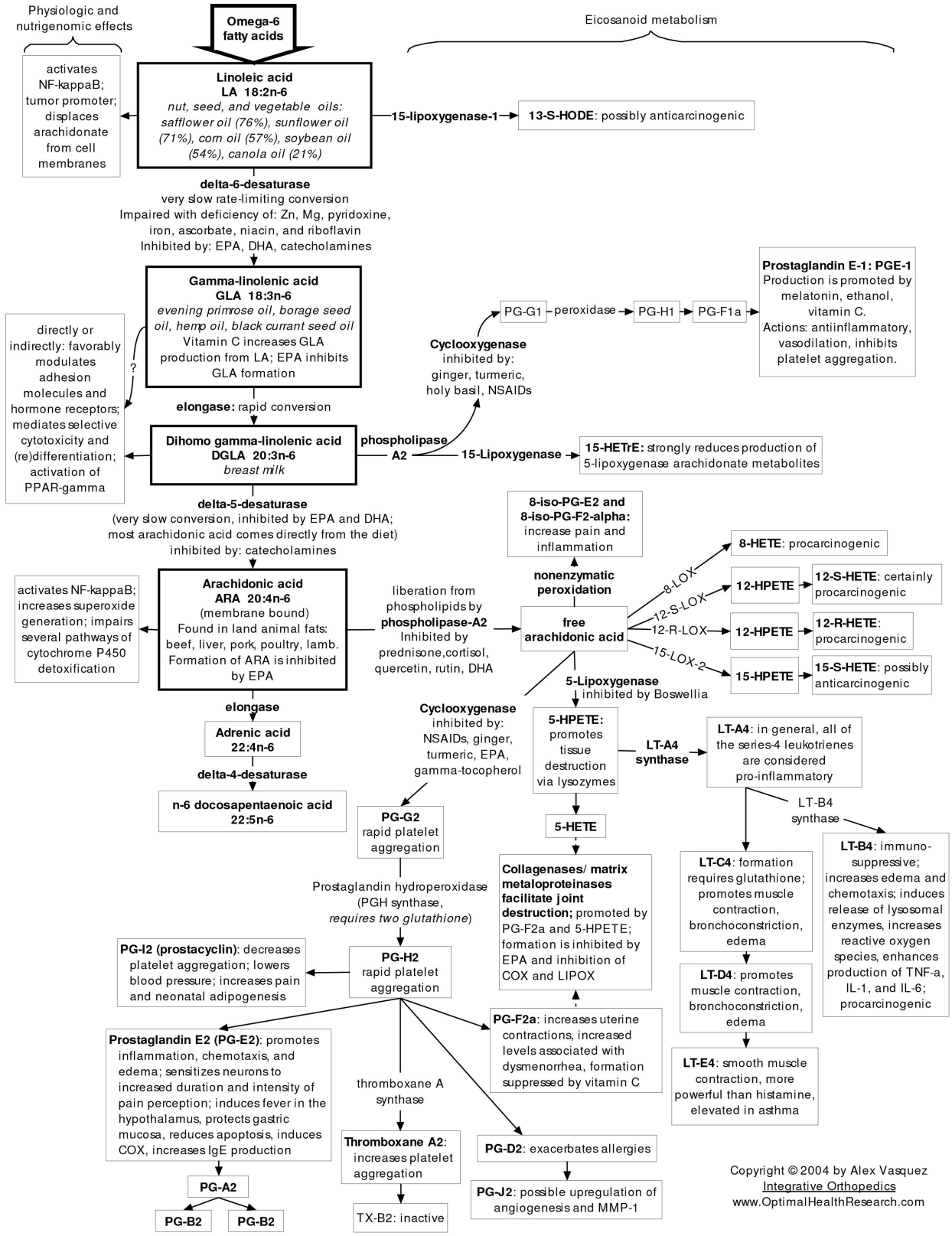


Figure 2. Metabolism of omega-6 fatty acids and related eicosanoids



THE HEALTH-PROMOTING FATTY ACIDS: ALA, EPA, DHA, GLA, AND OLEIC ACID

- ***Alpha-linolenic acid: ALA, α-LNA, ALNA, 18:3n3:*** ALA is an essential fatty acid as it is the "first in line" in the family of omega-3 polyunsaturated fatty acids (PUFA). Sources include flax seed oil (57% ALA), canola oil (9% ALA), soy oil, breast milk, English/black walnuts, soybeans, pine nuts, green vegetables, and beans. Conversion of ALA to the more biologically active EPA and DHA does not reliably or efficiently occur in humans.[26] No increase in DHA has been consistently observed in humans after supplementation of ALA[27]; in fact, supplementation with flax seed oil has actually been shown to reduce DHA levels in humans.[28] Although ALA can reduce blood pressure and cardiovascular mortality[26], it does not reduce serum lipids as do EPA and DHA. In a study of men with metabolic syndrome, ALA was shown to have anti-inflammatory benefits independent of its conversion to EPA or DHA.[29] The mechanism of action appears to be downregulation of NF-KappaB (the main "amplifier" for the expression of proinflammatory gene products[30]) rather than the direct modulation of eicosanoid biosynthesis. One study using flax oil as a source of ALA to treat rheumatoid arthritis found no clinical or biochemical benefit (i.e., no change in Hgb, CRP, ESR)[31]; however, the poor results of this study may have been due to the inferior quality of the flax oil product that was used which only supplied 32% ALA compared with the much higher concentration of 57% found in most products. Moderate intakes of ALA from flax oil profoundly reduce production of proinflammatory prostaglandins (e.g., PG-E2, measured by urinary excretion) by 52% to 85% in humans[32] which is superior to the 42% reduction induced by rofecoxib (the drug "Vioxx").[33] In summary, increased intake of ALA appears to provide cardioprotective[34] and anti-inflammatory benefits[29,32], and ALA can help reduce the frequency and severity of migraine headaches when used as part of a comprehensive natural treatment plan that includes diet change and nutritional supplementation.[35]
- ***Eicosapentaenoic acid: EPA, 20:5n3:*** EPA is essentially absent in vegan diets since the major dietary source is fish oil. Dietary EPA is incorporated into cell membranes where it modulates neurotransmitter and hormone receptor function and where it is stored before liberation by phospholipase for eicosanoid production. EPA-derived eicosanoids have anti-inflammatory properties, including a reduction in the production of proinflammatory eicosanoids such as LT-B4, PAFs, and cytokines such as TNF-alpha and IL-1, and a large reduction in PG-E2 and TX-B2.[36] Unfortunately, EPA can decrease production of DGLA, the metabolite of GLA that has health-promoting properties.[37] EPA doses of at least 4 grams per day are needed to increase bleeding time.[38] EPA supplementation reduces urinary excretion of calcium in patients with hypercalciuria and may therefore help prevent the development of calcium urolithiasis.[39] Due to its anti-inflammatory, membrane-enhancing, and other nutrigenomic benefits, EPA supplementation has proven beneficial for patients with lupus,[40] cancer[41], borderline personality disorder[42], mental depression[43, 44, 45], schizophrenia[46], and osteoporosis (when used with GLA).[47]
- ***Docosahexaenoic acid: DHA, 20:6n-3:*** DHA is found only in plants of the sea, phytoplankton/microalgae, and consumers of microalgae (such as fish). Like EPA, DHA is an important component of cell membranes and generally appears to improve cell membrane function via improving receptor function and signal transduction. In late 2003, bioactive metabolites of DHA—the docosatrienes and resolvins—were discovered to mediate potent anti-inflammatory benefits.[48] Animal studies have shown that induction of DHA deficiency causes memory deficits and a reduction in hippocampal cell size[49], and DHA deficiency in humans is consistently associated with mental depression, learning disorders (e.g., ADD/ADHD), and other neuropsychiatric disorders such as schizophrenia. DHA levels are reduced by ethanol consumption.[50] DHA appears essential for optimal cognitive function in infants and adults, and DHA also provides protection against thrombosis, arrhythmia, cardiovascular death, Alzheimer's disease[51], otitis media (when used with nutritional supplementation[52]), and coronary restenosis following angioplasty.[53] Supplementation with DHA (often in the form of fish oil, which includes EPA) has been shown to benefit patients with bipolar disorder[54], Crohn's disease[55], rheumatoid arthritis[56, 57, 58], lupus[59], cardiovascular disease[60], psoriasis[61], and cancer.[62] DHA appears to have an "anti-stress" benefit manifested by 30% reductions in norepinephrine and improved resilience to psychoemotional stress.[63, 64] Supplementation with EPA+DHA is extremely safe and reduces all-cause mortality.[60]
- ***Gamma (γ)-linolenic acid: GLA, 18:3n6:*** The

most powerful health-promoting n-6 fatty acid, GLA is found in varying concentrations in evening primrose oil, borage seed oil, hemp seed oil, and black currant seed oil. Most if not all of the actions of GLA are mediated following its elongation to the biologically active DGLA, from which eicosanoids that have cardioprotective and anti-inflammatory benefits are derived. Low levels of DGLA are associated with increased risk for stroke and myocardial infarction.[37] DGLA metabolites reduce the formation of the arachidonate-derived 2-series prostaglandins, 4-series leukotrienes and platelet-activating factor.[65] GLA supplementation results in the formation of two biologically active metabolites from DGLA formed by cyclooxygenase and lipoxygenase. Prostaglandin E-1 (PG-E1) is the main metabolite formed from DGLA by cyclooxygenase and its production is increased by vitamin C.[66] PG-E1 decreases platelet aggregation[37], inhibits vascular smooth muscle cell proliferation *in vitro*[67], causes vasodilation[36], and thus helps lower blood pressure.[37] PG-E1 has anti-inflammatory benefits and is probably the most potent prostaglandin with respect to bronchodilation.[66] Additionally, PG-E1 may have a mood elevating effect insofar as levels are elevated in patients with mania, reduced in patients with depression, and are elevated by ethanol intake.[68] Production of PG-E1 is increased by n-3 fatty acids.[69] 15-HETrE is the second main metabolite from GLA/DGLA and is formed from DGLA via 15-lipoxygenase. 15-HETrE has potent anti-inflammatory action by inhibiting the conversion of arachidonic acid to leukotrienes via inhibition of 5-lipoxygenase and 12-lipoxygenase.[37, 70] Clinically, this is very important because several common and serious health problems including allergy, asthma, cardiovascular disease, and cancer are at least partially dependent upon the function of lipoxygenase for the production of leukotrienes. Notably, prostate cancer cells can be rapidly killed *in vitro* by lipoxygenase inhibition.[71] Clinical benefit associated with GLA supplementation is seen in patients with, eczema[72], breast cancer (when used with tamoxifen[73]), premenstrual syndrome[74], rheumatoid arthritis[75, 76], diabetic neuropathy[77], migraine headaches (when used with ALA[35]), and respiratory distress syndrome (when used with EPA).[78]

- ***Oleic acid:*** N-9 oleic acid appears to have health-promoting benefits, namely cardioprotection and anti-inflammation which are both partially mediated via suppression of NF-kappaB.[79] Most studies that have used oleic acid have used olive oil, which is a complex mixture of oleic acid, squalene, and phenolic antioxidants/anti-inflammatories; therefore, determination of the benefits of oleic acid alone (i.e., without squalene and phenolics) is difficult. Other sources of oleic acid include flax seed oil and borage oil. Olive oil should be consumed in the diet to attain sufficient quantity of oleic acid along with the health-promoting, anti-inflammatory, anti-cancer, and cardioprotective squalene and phenolic antioxidants. Dietary consumption of olive oil is consistently associated with reductions in cancer and cardiovascular disease, particularly when used as a component of a health-promoting diet.[80, 81]

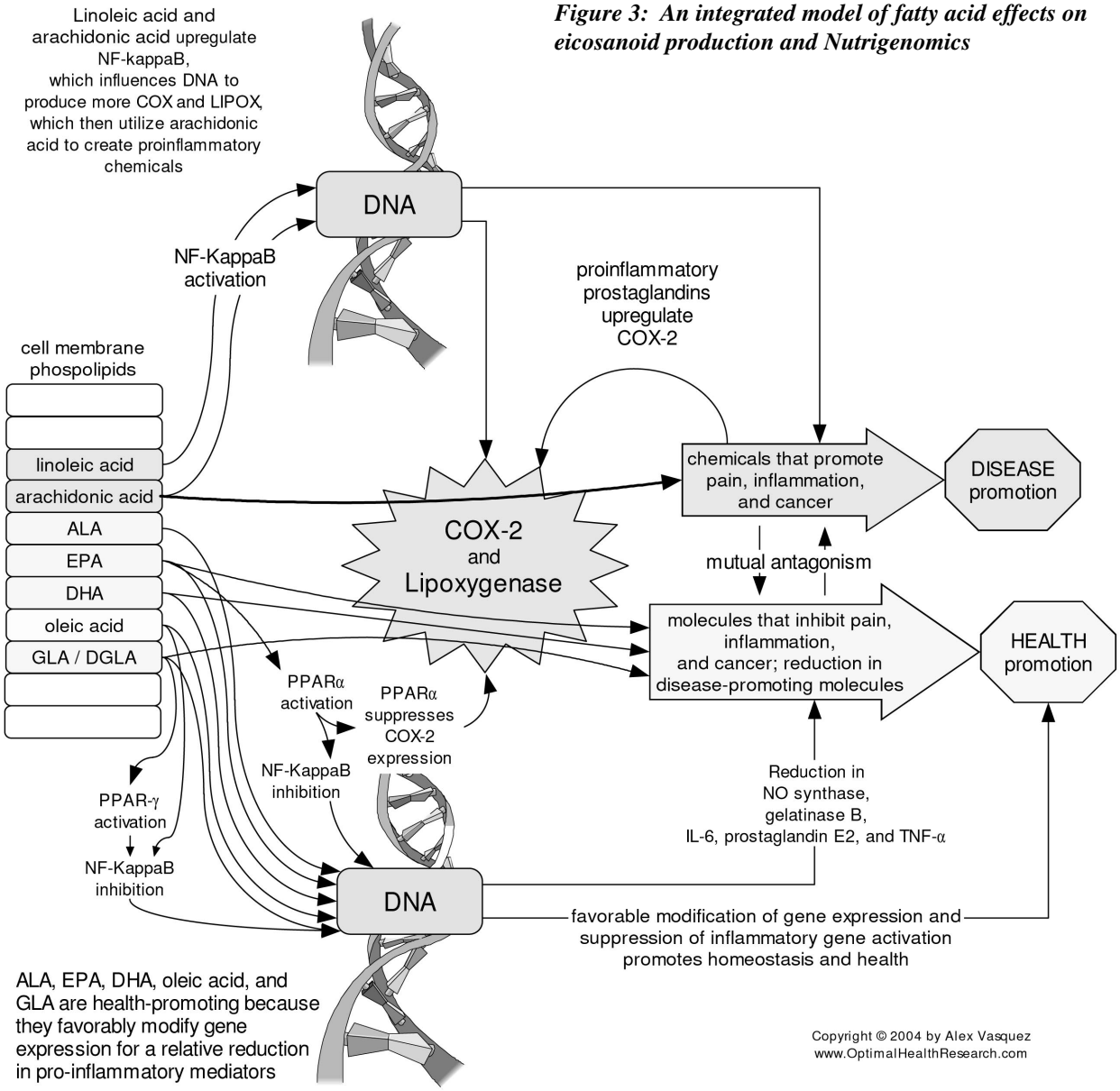
NUTRIGENOMICS: MODULATION OF GENETIC EXPRESSION VIA INTERVENTIONAL NUTRITION

The study of how dietary components and nutritional supplements influence genetic expression is referred to as "nutrigenomics" or "nutritional genomics" and has been described as "the next frontier in the postgenomic era."[82] Various nutrients have been shown to modulate genetic expression and thus alter phenotypic manifestations of disease by upregulating or downregulating specific genes, interacting with nuclear receptors, altering hormone receptors, and modifying the influence of transcription factors, such as proinflammatory NF-kappaB. Indeed, the previous view that nutrients only interact with human physiology at the metabolic/post-transcriptional level must be updated in light of current research showing that nutrients can, in fact, modify human physiology and phenotype at the genetic/pre-transcriptional level. Whereas pharmaceutical modulation of genetic expression will require billions of dollars and decades of research before clinical implementation, the power of health-promoting nutritional interventions is available to us immediately at comparatively negligible cost.

Fatty acids and their end-products modulate genetic expression in several ways, as these examples will illustrate. In general, n-3 fatty acids decrease inflammation and promote health while n-6 fatty acids (except for GLA, which is generally health-promoting) increase inflammation, oxidative stress, and the manifestation of disease. Corn oil, probably as a result of its high n-6 LA (linoleic acid) content, rapidly activates NF-kappaB and thus promotes tumor development, atherosclerosis, and elaboration of pro-inflammatory mediators such as TNFa.[83, 84, 85] Similarly n-6 arachidonic acid increased production of the free radical superoxide approximately 4-fold when added to isolated Kupffer cells *in vitro*. Prostaglandin-E2 is produced from arachidonic acid by cyclooxygenase and increases

genetic expression of cyclooxygenase and IL-6; thus, inflammation manifested by an increase in PG-E2 leads to additive expression of cyclooxygenase, which further increases inflammation and elevates C-reactive protein.[86] The unique health-promoting effects of GLA are nutrigenomically mediated via activation of PPAR-gamma, inhibition of NF-kappaB, and impairment of estrogen receptor function.[87, 88] Supplementation with ALA leads to a dramatic reduction of prostaglandin formation in humans[32], and this effect is probably mediated by down-regulation of proinflammatory transcription, as evidenced by reductions in CRP, IL-6, and SAA.[29] EPA appears to exert much of its anti-inflammatory benefit by suppressing NF-kappaB activation via activation of PPAR-alpha[89] and thus reducing elaboration of proinflammatory mediators.[90] EPA also indirectly modifies gene expression and cell growth by reducing intracellular calcium levels and thus activating protein kinase R which impairs eukaryotic initiation factor-2alpha and inhibits protein synthesis at the level of translation initiation, thereby mediating an anti-cancer benefit.[91] DHA is the precursor to docosatrienes and resolvins which downregulate gene expression for proinflammatory IL-1, inhibit TNFa, and reduce neutrophil entry to sites of inflammation.[48] Therefore, we see that fatty acids directly affect gene expression by complex and multiple mechanisms. These effects are summarized in Figure 3.

Figure 3: An integrated model of fatty acid effects on eicosanoid production and Nutrigenomics



BIOCHEMICAL AND CLINICAL SUPERIORITY OF USING FATTY ACIDS IN BALANCED COMBINATION

For the majority of clinical situations, the use of fatty acids in isolation is inferior to using fatty acids in balanced combination for several reasons. First, fatty acid defects/deficiencies generally occur *in combination* rather than in isolation, and therefore more than one fatty acid is generally needed when fatty acid supplementation is required. Second, since fatty acids compete for space in cell membranes, supplementation with a single fatty acid can exacerbate depletion of other fatty acids. Supplementation with EPA and DHA (ie, fish oil) leads to a reduction in DGLA and deprives patients of the benefits of PG-E1 and 15-HETrE[92]; therefore GLA should be supplemented when EPA and DHA are used. ALA supplementation[32] and fish oil supplementation[93] both reduce tissue levels of oleic acid and this is believed to have negative effects; therefore ALA and fish oil supplementation should include additional oleic acid. GLA supplementation causes a harmful reduction in EPA and a harmful increase in arachidonic acid unless EPA and DHA are supplemented along with the GLA.[94] Because of these adverse effects noted with the use of single sources of fatty acids, **the current trend in the research literature and in clinical practice is to use fatty acids *in combination*.** In other words, clinical benefits are generally improved significantly when doctors and patients use a fatty acid supplement that contains the health-promoting omega-3, -6, and -9 fatty acids *in combination* and *in their proper ratios*.

Clinical studies using mixed fatty acid preparations have shown clinically powerful benefits. The combination of ALA and GLA was shown to dramatically reduce the severity, frequency, and duration of migraine headaches when used with vitamin supplementation and a reduction in dietary arachidonate.[35] Combination therapy with EPA, DHA, GLA, and arachidonate was found beneficial for children with symptoms of ADD/ADHD.[95] Combination therapy with EPA and GLA improved biochemical and clinical indexes in adult patients with acute respiratory distress syndrome.[78] Supplementation with GLA, EPA, and calcium is superior to calcium alone in the treatment and prevention of osteoporosis.[47] In a recent placebo-controlled trial with pregnant women, the combination of EPA, DHA, and GLA appeared to protect women from eclampsia and edema.[96] Similarly, in patients with asthma, the combination of EPA and GLA was well tolerated and reduced leukotriene-B4 production.[97] Recently, the combination of EPA+DHA in a 2:1 ratio with GLA was estimated to reduce the risk for myocardial infarction in women by 43%.[98] Thus, using combinations of health-promoting fatty acids from the n-3 family (i.e., ALA, EPA, DHA) and n-6 family (i.e., GLA) along with n-9 oleic acid to prevent the decrease in oleic acid that occurs with ALA, EPA, and DHA supplementation will most certainly prove clinically beneficial for the treatment and prevention of an impressively wide range of health disorders; the research is already showing a clear trend in this direction.

CONCLUSIONS AND CLINICAL IMPLEMENTATION

Fatty acid imbalances and deficiencies are common in industrialized societies such as America that consume nutritionally deficient diets with a lack of vitamins, minerals, and n-3 fatty acids and a superabundance of artificial foods and over-reliance upon grains.[99, 100] The consistent theme in the research is that supplementation with ALA, EPA, DHA, GLA, and oleic acid provides clinically significant health-promoting benefits in a wide range of patient groups with various health disorders. In the treatment of inflammatory, cardiovascular, and malignant diseases, concomitant reduction in dietary arachidonic acid accentuates the benefits of ALA, EPA, DHA, and GLA supplementation.[101] Paradoxically, preservation of or an increase in tissue levels of arachidonic acid can be uniquely beneficial in patients with neuropsychiatric illness such as depression, attention deficit / hyperactivity disorder, and schizophrenia when treated with fatty acid supplementation.[95, 102, 103]

The safety of fatty acid supplementation is high and has been well established in numerous clinical studies. Drug interactions are extremely rare with fatty acids. The low frequency of drug interactions and adverse effects is to be expected from these fatty acids which are synthesized within the body and/or available from common foods, though in insufficient amounts to be clinically therapeutic. Very high doses of n-3 fatty acids may have a clinically significant anticoagulant effect and should be used cautiously in patients with bleeding tendencies and those taking anticoagulant medications such as coumadin/warfarin, aspirin, or plavix/clopidogrel.

Supplementation with ***all*** of the health-promoting fatty acids—ALA, EPA, DHA, GLA, and oleic acid—is expected to provide doctors and patients with benefits superior to those attained with the use of single fatty acids in isolation. Doses are tailored to patient size/weight and health status and are kept within the safe boundaries established in published research. Oleic acid is safe at high doses as its is consumed *ad libitum* in Mediterranean diets. The highest daily dose of ALA reported in the literatures is 10,700 mg used in a 4-week study of lactating women.[27] Two studies have used 13,000 mg EPA+DHA per day without adverse effects in hypertensive patients[104] and cancer patients.[105] Four grams per day of GLA has been safely

used in adults, and proof of safety was established in a study of infants with eczema given doses of 3 grams per day.[72] Clinical effectiveness of fatty acid supplementation for most conditions (e.g., cancer and all inflammatory/ autoimmune diseases) will be increased by implementing a diet low in linoleic and arachidonic acids, which is achieved via avoidance of vegetable oils, nut oils, milk/dairy, and most grain-fed beef, liver, pork, lamb, and, to a lesser extent, turkey and chicken. Food allergens are avoided and the underlying immune dysfunction is addressed with orthomolecular immunomodulation.[25] Balanced, complete fatty acid supplementation along with a health-promoting diet[24,25], multivitamin supplementation[106], and assurance of optimal vitamin D status[25,107] forms the foundational treatment plan for nearly all patients with all diseases. For many patients, regardless of their official "diagnosis", this simple, safe, cost-effective approach of overall health improvement is all the treatment they require. Doctors who use this approach will have achieved a significant clinical advantage in the treatment of patients with premenstrual syndrome, diabetic neuropathy, respiratory distress syndrome, Crohn's disease, lupus, rheumatoid arthritis, cardiovascular disease, hypertension, psoriasis, eczema, migraine headaches[108], bipolar disorder[109], borderline personality disorder, mental depression[110] schizophrenia, osteoporosis[111], polycystic ovary syndrome[112], multiple sclerosis[113], and musculoskeletal pain.[25,114,115] Patients with highly complex illnesses and multiple health disorders may require additional treatment, as will be described in future articles in this journal following a comprehensive synthesis of current research for chiropractic and naturopathic physicians.[25]

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