Dynamic Chiropractic

Essential Fatty Acids and Eicosanoids

THEIR ROLE IN PREVENTING INFLAMMATION, CARDIOVASCULAR DISEASE AND CANCER

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Eicosanoids are molecules produced by most tissues in the body known to exert hormone-like effects on the cells that produce them (autocrine effects), as well as on neighboring cells (paracrine effects). Research over the past 30 years reveals that various types of eicosanoids influence biological steps involved in the prevention and promotion of inflammatory states, cardiovascular disease and cancer. Of the utmost importance is the fact that eicosanoid synthesis is largely dictated by the ingestion of various types of dietary polyunsaturated fats, which give rise to the prevention (or suppression) of inflammatory states (including arthritis), cardiovascular disease and cancer. However, the ingestion of other, less desirable polyunsaturated fatty acids has been shown to promote inflammation, cardiovascular disease and cancer. As such, specific dietary practices and the use of targeted dietary supplements should be viewed, by individuals and health practitioners, as extremely important interventions in the prevention and management of these prevalent health conditions.[1-4]

Important Classes ofEicosanoids

Eicosanoids are derived from dietary polyunsaturated fatty acids, which are incorporated as esters into the phospholipids and diacylglycerols found in the cell membrane and nuclear membrane. Eicosanoids are not stored within cells, but are synthesized as required and rapidly inactivated. They are potent in the nanomolar range.

The initiation of eicosanoid biosynthesis occurs when a cell is stimulated or influenced by mechanical trauma, cytokines (released by immune cells), growth factors or other stimuli. The stimulus may even be an eicosanoid from a neighboring cell. This promotes the release of a phospholipase enzyme at the cell membrane, which travels to the nuclear membrane, where it catalyzes a reaction (hydrolysis) that releases a 20-carbon polyunsaturated fatty acid. This hydrolysis appears to be the rate-determining step for eicosanoid formation. As such, the activities of phospholipase enzymes play a prominent role in the eicosanoid synthesis and the disease states influenced by eicosanoids.[1-4]

Of interest is that one of the effects of corticosteroid drugs, such as prednisone, is that they inhibit phospholipase A_2 activity. Thus, the synthesis of pro-inflammatory eicosanoids is suppressed in the conventional management of a variety of complex inflammatory conditions (e.g., rheumatoid arthritis). Unfortunately, corticosteroid drug administration is associated with significant side effects such as hypertension, thrombophlebitis, thromboembolic events, glucose intolerance and aggravation of diabetic states, hypokalemia, hypocalcemia, bone demineralization, sodium and fluid retention, metabolic alkalosis, weakened immunity, skin eruptions, impaired wound healing, skin thinning, peptic ulcer, pancreatitis, ulcerative colitis and other problems. For this reason, monitoring patients is imperative during corticosteroid use, and medical practitioners are instructed to recommend these drugs with extreme caution.[5]

With respect to eicosanoid synthesis, once released from cell membrane phospholipids by phospholipase A_2 ($cPLA_2$) enzyme, the 20-carbon polyunsaturated fatty acids are converted into either prostanoids (prostaglandins, prostacyclins or thromboxanes) by a cyclooxygenase enzyme, or into leukotrienes by a lipoxygenase enzyme. The 20-carbon fatty acids that are converted into these classes of eicosanoids include arachidonic acid, dihomo-gamma linolenic acid (both omega-6 fats) and eicosapentaenoic acid (an omega-3 fat). In the overall scheme of things, arachidonic acid (AA) is converted into prostanoids and leukotrienes that promote inflammation, cardiovascular disease and cancer. Conversely, dihomo-gamma linolenic acid (DGLA) and especially eicosapentaenoic acid (EPA) are converted into prostanoids and leukotrienes that suppress inflammatory events, cardiovascular disease and cancer.[1-4]

Dietary and Supplemented Essential Fatty Acidsand Eicosanoid Synthesis

Of interest to this discussion is the fact that linoleic acid (LA), an omega-6 fatty acid commonly found in corn oil, sunflower seed oil, safflower seed oil and mixed vegetable oils, has been shown to be desaturated and elongated by enzymes within the human body to form AA. Arachidonic acid itself is found in high concentrations of high-fat animal meats, such as red meat and pork, as well as any milk or yogurt product higher than 1 percent milk fat and any cheese higher than 3 percent milk fat. This list would extend of course to ice cream, whipped cream, cream, cream cheese, regular sour cream, etc.

The North American diet, with its high animal-fat content and generous use of oils rich in LA, provides cells with generous amounts of polyunsaturated fats (AA) from which to produce prostanoids and leukotrienes that promote inflammation, cardiovascular disease and cancer. The key point here is that DGLA and EPA directly compete with AA for conversion to less harmful prostanoids and leuko-trienes. Higher cellular concentrations of EPA and DGLA, and lower cellular concentrations of LA and AA, result in greater synthesis of inflammation-suppressing eicosanoid production. This is because AA, DGLA and EPA all compete with each other for activation by cyclo-oygenase and lipoxygenase enzymes. As such, a simple dietary and supplementation strategy to enrich cellular concentrations of EPA and DGLA involves regular consumption of fatty fish [for EPA and docosahexaenoic acid (DHA)], and supplementation with a combination of flaxseed oil [for alpha-linolenic acid (ALA), which the body can desaturate and elongate into EPA], fish oil (for EPA and DHA) and borage seed oil [for gamma-linolenic acid (GLA), which the body converts into DGLA].

It also should be noted that ALA competes with LA for the elongase and desaturase enzymes for conversion to EPA. In turn, this blocks the conversion of LA into AA. Thus, flaxseed oil supplementation not only provides raw materials from which the body can make EPA, (as well as DHA, which is important for vision and brain function throughout life); ALA also helps to decrease membrane concentrations of AA by blocking the conversion of LA into AA. (LA is oversupplied by the North American and Western diet.) Thus, this lack of conversion helps the synthesis of health-promoting eicosanoids and the suppression of inflammation-promoting eicosanoids.[1-4]

Eicosanoids of Importancein the Disease Process

Although the body makes nu-merous types of eicosanoids (some of which have no known physio-logical function at this time), there are several which have been shown to significantly impact the prevention or promotion of various health conditions.

Inflammation: In regard topromotion of inflammation, prostaglandin E_2 (PGE-2), formed from activation of AA by cyclooxygenase, acts inside the cell to produce various types and quantities of

cytokines, which are pro-inflammatory agents that bring active leukocytes to the injury site. Many leukocytes (white blood cells) convert AA into pro-inflammatory leukotrienes via 5-lipoxygenase enzyme, such as pro-inflammatory leukotriene B_4 (LTB_4), which makes local blood vessels more permeable.

In turn, plasma leaks out into the connective tissues, causing more swelling. PGE_2 also sensitizes pain-nerve endings, increasing pain from the inflamed tissues.

In contrast to this, DGLA yields PGE_1, which powerfully counteracts PGE_2, toning down the inflammatory response. The body slowly synthesizes DGLA from LA (LA>GLA>DGLA). However, conversion slows down as we age, allowing inflammatory states to occur more easily. In this regard, many health experts recommend daily supplementation with 800-1,200 mg of borage seed oil (which is 22 percent GLA, compared to only 9 percent GLA in evening primrose oil). DGLA also yields the leukotriene LTB_5, which counters the inflammatory action of the AA-derived LTB_4.

EPA acts as a precursor for pro-staglandin-3 and promotes the synthesis of leukotriene-5 groups, all of which suppress the inflammatory response. It is noteworthy that the body can synthesize EPA from both ALA and DHA.[6,7,8]

Cardiovascular disease: In regard to cardiovascular disease, a prostanoid synthesized from AA via cyclooxygenase (namely thromboxane A_2) increases risk of cardiovascular disease by constricting blood vessels, increasing smooth muscle tone and by increasing platelet coagulation. Platelet coagulation, forming a plug in the artery wall (in the area of atherosclerosis development), is often the final precipitating event leading to a myocardial infarction, angina or other ischemic vascular event. Thromboxane A_2 is synthesized with platelets. Interestingly, endothelial cells in the blood vessel wall synthesize an anti-platelet aggregatory protanoid from AA, known as prostacyclin I-2 (PGI_2). However, high tissue concentrations of AA tend to produce a strong vasoconstriction response and enhance platelet aggregation due to the synthesis of thromboxane A_2. This generally supersedes the anti-aggregatory influence of endothelial-derived PGI_2. However, higher tissue levels of EPA permits the anti-aggregation effects of PGI_2 to be expressed with greater influence, helping to reduce the risk of many ischemic cardiovascular events.

EPA inhibits synthesis of thromboxane (TXA_2) and leukotriene B-4 (LTB_4) by platelets and macrophages. Reduction of the pro-aggregatory, vasoconstrictive TXA_2 decreases the thrombotic tendency of platelets, reducing risk of cardiovascular disease. This is augmented by the limited depression of the vasoactive anti-aggregatory prostacyclin (PGI_2) secreted by endothelial cells and the generation of anti-aggregatory prostaglandin I-3 (PGI3) from EPA. EPA has been shown to reduce blood pressure and blood viscosity and modulate membrane fluidity and associated enzyme and receptor functions. The collective effects of omega-3 fatty acids likely account for the reduction in coronary arterial disease in populations consuming foods rich in omega-3 fatty acids.[1,2,3,9,10,11,12]

Cancer: Abundant evidence suggests that the conversion of AA into various leukotrienes via the 5-lipoxygenase enzyme and the 12-lipoxygenase enzymes has a profound influence on the development and progression of human cancers. Compared with normal tissues, significantly elevated metabolites of the lipoxygenase pathway (using AA as the essential fatty acid), are common features in lung, prostate, breast, colon and skin cancers, as well as in cells from patients with both acute and chronic leukemia.

Lipoxygenase end-products derived from AA (especially leukotriene A_4 and 5-

hydroxyeicosatetraenoic acid) elicit diverse biological activities required for neoplastic cell growth. They influence cellular growth factors, transcription factor activation (which up-regulates oncogenes) and oncogene induction. They also help to inhibit programmed cell death (apoptosis) and influence other factors important for cancer cell survival, progression and metastasis. As well, prostanoids derived from AA have been shown to stimulate cell proliferation, which increases risk for cancer development and promotes proliferation of existing (possibly latent) cancer cells.[13] In recent years, it has been recognized that certain nonsteroidal, anti-inflammatory drugs (NSAIDs), such as aspirin, may reduce risk of colon and other cancers by blocking the action of cyclooxygenase enzyme. In turn, this inhibits the synthesis of PGE_2 and other prostanoids formed from AA, which are involved in inflammation, platelet aggregation, vasoconstriction and cellular proliferation.

In this regard, NSAIDs have been used to reduce inflammation, pain and fever, as well as to reduce platelet stickiness in an effort to reduce risk of coronary disease. Experimental and epidemiological studies recognize that these drugs also may offer protection against certain cancers by slowing cellular proliferation.[14,15] However, NSAIDs also increase risk of gastrointestinal bleeding, ulcers, liver and kidney toxicity, and may hasten the progression of cartilage erosion in osteoarthritis. In fact, 10,000 to 20,000 individuals die each year in the United States from bleeding disorders (and other complications) induced by the frequent use of NSAIDs. As such, their application as prophylactic agents in cancer prevention may place individuals at risk for other life-threatening health conditions.[16,17,18]

Of interest to natural health practitioners is the fact that certain natural agents such as the flavonoid baicalein (from Chinese skullcap) and curcumin (from the spice turmeric) have been shown to block the 12-lipoxygenase enzyme. Experimental, preclinical and preliminary studies indicate that these natural compounds are able to suppress cancer development and block the recurrence of cancer in colon cancer patients.[13] Moreover, other natural agents have been shown to block cyclooxygenase without disrupting platelet function or causing bleeding disorders or organ toxicity. Highly effective agents include curcumin, white willow extract, ginger, boswellia and quercetin. Each of these natural compounds has been used to effectively treat a variety of joint inflammatory conditions and also may hold promise as natural interventions to help prevent cancer by blocking the conversion of AA to prostanoid metabolites (cyclooxygenase inhibition).[19-31]

At the same time, epidemiological studies, prospective studies and experimental studies suggest higher tissue concentrations of omega-3 fatty acids, and lower tissue concentrations of AA and LA are associated with decreased cancer incidence.[32-36] EPA gives rise to metabolites, which have shown to inhibit cancer development, including mice with transplantable human breast cancer consisting of the genetic phenotype (HER-2/neu) that afflicts 15 percent to 40 percent of all human breast cancer patients. EPA also has been shown to compete with AA for activation via the lipoxygenase enzyme system, helping to reduce AA-derived metabolites that spur the growth and spread of cancer.[4]

Summary

Although day-to-day choices around diet and nutritional supplements do not often feel like life-and-death decisions, the evidence suggests that nutritional components account for as much as 35 percent of all cancers,[37] affect many risk factors for cardiovascular disease (e.g., cholesterol, triglycerides, homocysteine, blood pressure, eicosanoids),[3] and modulate reactions associated with

joint inflammation, autoimmune conditions and other inflammatory states.[6,7] Cancer and cardiovascular disease alone account for approximately 70 percent of deaths each year, and many thousands of individuals suffer from arthritis and other inflammatory conditions that compromise quality of life. This article has drawn attention to the impact that polyunsaturated fatty acid consumption has on the eicosanoid cascade, and the effect that various eicosanoids have on these prevalent health conditions.

Based on the available evidence, I recommend that health practitioners encourage their patients to do the following:

- limit their intake of foods rich in AA and LA;
- consume fish two to three times per week (more than this may increase risk of mercury toxicity); and
- supplement their daily diet with an essential fatty acid supplement containing 400 mg each of borage seed oil, flaxseed oil and fish oil (ensuring a 30/20 percent contribution of EPA/DHA, respectively). For general prevention and wellness, individuals should consider two or three capsules per day. Individuals with certain health problems may require higher, more therapeutic doses.

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