Essential Fatty Acid Supplementation: Why the combination of flaxseed, borage seed and fish oil is the optimal blend for the heart, brain, joints and the prevention of cancer

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In Brief

Recent research confirms the findings of previous investigations, indicating that the synergistic action of essential fatty acids, richly supplied by flaxseed oil, borage seeed oil and fish oil, encourage the production of eicosanoids (mini-local hormones) that help defend the body against heart attack, stroke (and other cardiovascular diseases), control blood pressure, reduce joint inflammation, reduce the incidence of age-related dementia, and reduce risk of cancer development. Essentially, the polyunsaturated fatty acids, richly supplied by these oils, provide the body with the building blocks from which our cells make specific prostaglandins, prostacyclins, thromboxanes and leukotrienes (collectively known as eicosanoids, which act like local hormones) that strongly influence tissue behaviour and cellular function.

Whereas the polyunsaturated fatty acids supplied by foods high in animal fat, as well as certain types of vegetable oils that are high in linoleic acid, promote the formation of disease-promoting, inflammation-inducing eicosanoids, a lower animal fat diet, in conjunction with monounsaturated fatty oils (e.g. olive oil) accompanied by daily supplementation with flaxseed, borage seed and fish oil (totalling 2400-3600 mg per day, consisting of equal quantities of each oil) promotes the formation of eicosanoids that reduce risk of many diseases, suppress inflammatory states and help preserve cognitive function as we age.

Introduction

Eicosanoids are molecules produced by most tissues in the body and are known to exert hormone-like effects on the cells that produce them (autocrine effects), as well as on neighboring cells (paracrine effects). Research initiatives over the past 30 years reveal 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, such that ingestion of certain polyunsaturated fats gives rise to eicosanoids involved in the prevention (or suppression) of inflammatory states (including arthritis), cardiovascular disease and cancer, whereas the ingestion of other less desirable polyunsaturated fatty acids have 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 of Eicosanoids: Prostaglandins, Prostacyclins, Thromboxanes and Leukotrienes

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 and have a half-life ranging from seconds to minutes.

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 polyunsaturared fatty acid. This hydrolysis appears to be the rate-determining step for eicosanoid formation. As such, the activityof phospholipase enzymes play a prominent role in the eicosanoid synthesis, and the disease states influenced by eicosanoids. **(1-4**)

Of interest is the fact that one of the effects of corticosteroid drugs, such as prednisone, is that they inhibit phospholipase A_2 activity, thereby, suppressing the synthesis of pro-inflammatory eicosanoids in the conventional management of a variety of complex inflammatory conditions (e.g. rheumatoid arthritis, other autoimmune conditions etc). Unfortunately, corticosteroid drug administration is associated with a diverse array of 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, patient monitoring is imperative during corticosteroid use and medical practitioners are instructed to recommend these drugs with extreme caution. **(5)**

In regards to this matter, it has been shown that eicosapentaenoic acid (EPA) inhibits phospholipase A_2 release of AA from cell membrane, which is one additional means by which omega-3 fats have been shown to reduce the inflammatory response. **(42)**

With respect to eicosanoid synthesis, once released from cell membrane phospholipids by phospholipase A_2 ($cPLA_2$) enzyme, the 20-carbon polyusaturated 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 (an omega-6 fat), dihomo-gamma linolenic acid (an omega-6 fat) and eicosapentaenoic acid (an omega-3 fat). In the overall scheme of things arachidonic acid (AA) is converted into prostanoids and leukotrienes that that promote inflammation, cardiovascular disease and cancer, whereas dihomo-gamma linolenic acid (DGLA) and especially eicosapentaenoic acid (EPA) are converted into prostanoids and leukotrienes that suppress inflammatory events, cardiovascular disease and the promotion of cancer. **(1-4)**

Dietary and Supplemented Essential Fatty Acids and 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, mixed vegetable oils and other oils, has been shown to be de-saturated and elongated by enzymes within the human body to form AA. Arachidonic acid (AA) itself is found in high concentrations in high fat animal foods, such as red meat and pork, as well as any milk or yogurt product higher than 1% milk fat and any cheese higher than 3% milk fat. This list would extend of course to ice cream, whipped cream, cream, cream cheese, regular sour cream etc. As such, the North American diet, with its high animal fat content and generous use of oils rich in linoleic acid, 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 and more health-promoting prostanoids and leukotrienes, such that higher cellular concentrations of EPA and DGLA and lower cellular concentrations of LA and AA, result in a greater synthesis of health-promoting/ inflammation suppressing eicosanoid production and a reduced synthesis of the dangerous and inflammation-provoking eicosanoids made from AA. 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 (a rich source of EPA and docosahexaenoic acid – DHA), and supplementation with a combination of flaxseed oil (a rich source of alpha-linolenic acid - ALA, which the body can de-saturate and elongate into EPA), fish oil (a rich source of EPA and DHA) and borage seed oil (a rich source of gamma-linolenic acid – GLA, which the body converts into DGLA).

It should also be noted that ALA competes with LA for the elongase and de-saturase enzymes for its conversion from ALA to EPA. In turn, this blocks the conversion of LA into AA. Studies show that ALA displaces LA from the elongase and desaturase enzymes that produce AA. Thus, flaxseed oil supplementation not only provides raw materials from which the body can make EPA (as well as DHA, which can be made from EPA – DHA is important for vision and brain function throughout life), but ALA also helps to decrease membrane concentrations of AA by blocking the conversion of LA (which is oversupplied by the North American and Western diet) into AA, and thus helps promote the synthesis of health-promoting eicosanoids, and helps suppress the synthesis of disease and inflammation-promoting eicosanoids. **(1,2,3,4,41)**

Eicosanoids of Importance In The Disease Process

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

Inflammation: In regards to promotion of inflammation, prostaglandin E_2 (PGE-2) – formed from activation of AA by cyclo-oxygenase, acts inside the cell to produce various

types and quantities of cytokines, which are pro-inflammatory agents that complete the process by bringing 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 B4 (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 the sensation of 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 synthesis DGLA from LA (LA-------GLA-------DGLA), however, as we age this conversion slows down, allowing inflammatory states to occur more easily. In this regard many health experts recommend daily supplementation with 800-1200 mg of borage seed oil (which is 22% GLA compared to only 9% GLA supplied by 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 prostaglandin-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.

As noted above EPA also inhibits the action of phospholipase A_2, resulting in less AA being recruited into the pro-inflammatory cascade, and thus providing greater substrate concentration of EPA and DGLA to be activated cyclo-oxygenase and lipoxygenase for conversion into anti-inflammatory eicosanoid mediators. **(42)**

Investigative studies also indicate that although DGLA forms no leukotrienes via the lipoxygenase pathway, derivatives of DGLA have been show to block the conversion of AA to inflammatory leukotrienes, thereby reducing the inflammatory response. **(43)**

In summary, DGLA and EPA participate in biochemical cascades that parallel and compete with the arachidonic acid cascade. EPA provides the most important competing cascade. DGLA provides a third, less prominent cascade. These two parallel cascades (from EPA and DGLA) soften the inflammatory effects of AA and its products. Low dietary intake of these less-inflammatory essential fatty acids, has been linked to several inflammation-related diseases. **(6,7,8)**

Cardiovascular Disease: In regards to cardiovascular disease, a prostanoid synthesized from AA via cyclo-oxygenase, 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 tends to produce a strong vasoconstriction response, and enhances platelet aggregation due to the synthesis of

thromboxane A_2, which generally supercedes 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 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 (PGI_3) 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).**

Additionally, a study published in 2007 showed that supplementation with flaxseed oil significantly lowered blood pressure in patients with dyslipidemia compared to subjects supplemented with safflower seed oil; an oil rich in linoleic acid (LA). This study adds to the body of evidence that ALA (from flaxseed oil) is efficiently converted into EPA within the body, facilitating enhanced production of eicosanoids that dilate blood vessels, which decrease peripheral resistance to blood flow, reducing high blood pressure. **(38).** A previous study (Zhao G et al 2004) also demonstrated that dietary alpha linolenic acid (ALA) reduced inflammatory and lipid cardiovascular risk factors in hypercholesteolemic men and women. **(39)** In conjunction with animal studies these studies further substantiate the level of efficiency in which the body is able to convert ALA into EPA. **(40)**

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 leukemias. Lipoxygenase end-products derived from AA (especially leukotriene A_4 and 5-hydroxyeicosatetraenoic acid) have been shown to elicit diverse biological activities required for neoplastic cell growth. They influence cellular growth factors, transcription factor activation (which up-regulates oncogenes), oncogene induction, 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 also 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 non steroidal anti-inflammatory drugs, such as aspirin, may reduce risk of colon cancer and other cancer by blocking the action of cyclo-oxygenase

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 non steroidal anti-inflammatory drugs have been used to reduce inflammation, pain and fever, as well to reduce platelet stickiness in an effort to reduce risk of coronary disease. Experimental and epidemiological studies recognize that these drugs may also offer protection against certain cancers by slowing cellular proliferation. **(14,15).** However, non steroidal anti-inflammatory drugs also increase risk of gastro-intestinal 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 non steroidal anti-inflammatory drugs. As such, their application as prophylactic agents in cancer prevention may place individuals at risk for other dire and 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 cyclo-oxygenase 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 have been used to effectively treat a variety of joint inflammatory conditions, and may hold promise as natural interventions to also help prevent cancer by blocking the conversion of AA to prostanoid metabolites (cyclo-oxygenase inhibition). **(19-31)**

At the same time epidemiological studies, prospective studies and experimental studies suggest that higher tissue concentrations of omega-3 fatty acids and lower tissue concentrations of AA and LA is 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), which is the type that afflicts 15-40% of all human breast cancer patients. EPA has also 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)**

Brain Function

Several recent studies have suggested that higher intake and blood levels of omega-3 fatty acids may help to reduce risk of age-related cognitive decline, dementia and Alzheimer's disease. **(44-47)** Several mechanisms have been proposed to explain how omega-3-fats can reduce nerve cell degeneration associated with these conditions.

Omega-3 fatty acids are known to provide anti-inflammatory effects due to their conversion to anti-inflammatory eicosanoids within the body. The eicosanoids formed from omega-3 fatty acids also improve blood flow by dilating vessels, and decreasing platelet stickiness (anti-thrombotic), and provide other benefits associated with cardiovascular health, such as improving endothelial function and lowering triglyceride blood levels. All of these effects are also associated with prevention of cognitive decline largely via preserved blood flow circulation to brain tissue (lower risk of cerebrovascular disease).

However, omega-3 fatty acids also play a direct role in nerve cell structure and function. Eicosapentaenoic acid (EPA) and docsahexaenoic acid (DHA) have been shown to improve the composition of nerve cell membranes, and stimulate the development, regeneration and function of nerve cells by stimulating synaptic plasticity and increasing neurotransmission, as well as increasing memory abilities. In short, long chain omega-3 fatty acids are structural components of neuronal and other cell membranes, affecting membrane fluidity, nerve transmission and nerve cell function in a positive way. They also modulate the production of eicosanoids and inflammatory cytokines and help preserve blood flow to the brain.

There is also the suggestion that oxidative stress (from oxygen and other free radicals), significantly contributes to neuronal damage seen in cases of cognitive impairment and Alzheimer's disease, by depleting the brain of vulnerable highly unsaturated fatty acids (e.g. EPA and DHA). Some researchers suggest that by replenishing brain cells with EPA and DHA via higher intake levels, individuals may help protect themselves against cognitive decline to a significant degree. **(48,49,50)**

Adding support to the epidemiological and experimental studies that suggest that omega-3 fatty acids can reduce risk of cognitive decline, the April 2007 issue of the *American Journal of Clinical Nutrition* contained the findings of two large prospective studies that evaluated intake of omega-3 fatty acids and subsequent risk of cognitive decline, dementia and Alzheimer's disease in older human subjects. Taken together, the findings of MA Beydoun et al (the *Atherosclerosis Risk in Communities Study*) and those of BM van Gelder et al (the *Zutphen Elderly Study*) indicate that a moderate intake of EPA and DHA were strongly associated with reduced risk of cognitive decline.

The ARIC Study

The *Atherosclerosis Risk in Communities Study* analyzed plasma fatty acids in cholesterol esters and phospholipids in whites residing in Minneapolis MN from 1987 through 1989. From 1990 through 1992 and from 1996 through 1998, 3 neurophysiological tests were administered. Effectively, this study studied the association between plasma fatty acids and cognitive decline in adults aged 50-65 years of age at baseline and conducted a subgroup analysis. A striking finding among the 2251 study subjects was that higher levels of omega-3 fatty acids were associated with reduced risk of decline in verbal fluency, particularly in hypertensive and dyslipedemic subjects, whose tissues are exposed to greater oxidative stress from these conditions. In contrast, the risk of global cognitive decline increased with elevated palmitic acid (a saturated fat) and in subjects with higher levels of arachidonic acid (an omega-6 fatty acid found in meat and dairy products). **(51)** It should be noted that palmitic acid is a saturated fat that is highly

associated with thrombosis and the elevation of LDL-cholesterol, both of which can lead to atherosclerosis obstruction, increasing the tendency to develop dementia. **(52)**

The Zutphen Elderly Study

> In the *Zuthen Elderly Study* data on fish consumption of 210 male participants, who were aged 70-89 years of age in 1990, and data on cognitive functioning collected in 1990 and 1995 were assessed. The intake of EPA and DHA was calculated for each participant. Results showed that fish consumers had significantly less 5-year subsequent cognitive decline than did non fish consumers and a linear trend (dose-dependent trend) was observed for the relation between the intake of EPA and DHA and cognitive decline. More specifically, the results showed that elderly men who consumed an average of approximately 400 mg per day of omega-3 fatty acids from EPA and DHA had significantly less cognitive decline over the five year period than did those consuming an average of approximately 20 mg per day of omega-3 fatty acids.

At present the American Heart Association recommends the consumption of fish (preferably fatty fish) at least twice per week, a recommendation that is compatible with the results of the Zutphen Elderly Study. To achieve 400 mg per day of EPA and DHA, one would have to consume 6 servings per week of lean fish (average serving size 140 gm or about 5 ounces) or one serving per week of fatty fish, such as mackerel or herring. (10) One can also achieve this level of intake by consuming a mere 20 gm of Chinook salmon (less than one ounce) or 100 gm of cod (a little more than 3.5 ounces). As such, two to three meals of fish per week would supply approximately 380 mg of EPA/DHA per day, on average.

The *Zutphen Elderly Study* highlighted the fact that an average daily intake of 400 mg of EPA and DHA appears to be a significant threshold level at which a marked protective effect is observed. Some experts suggest that for people who are allergic to fish and/or shellfish and those who cannot or will not obtain sufficient intake of fish, that they consume 1000 mg per day of fish oil from supplementation (Connor WE, Connor SL, 2007). **(53)** A supplement containing fish oil and flaxseed oil may also be a consideration providing the total amount of EPA and DHA reaches a minimum threshold intake value of 400 mg per day. Health practitioners should bear this information and these dosage levels in mind when making recommendations about specific essential fatty acid supplement products to their patients in regards to optimizing brain function.

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% of all cancers **(37),** affect many risk factors for cardiovascular disease (e.g. cholesterol, triglycerides, homocysteine, blood pressure, eicosanoids) **(3),** and

modulate inflammatory reactions associated with joint inflammation, autoimmune conditions and other inflammatory states. **(6,7)** Cancer and cardiovascular disease alone account for approximately 70% of deaths each year and many thousands of individuals suffer from arthritis and other inflammatory conditions that compromise quality of life indices. In addition, recent evidence demonstrates that sufficient ingestion of omega-3 fatty acids is also required to inhibit the development of age-related cognitive decline. 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 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 diet daily with an essential fatty acid supplement containing 400 mg each of borage seed oil, flaxseed oil and fish oil (ensuring a 30/20% 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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