The Role of Essential Fatty Acids in Health and Disease

Since the discovery in 1963 that unsaturated fatty acids are converted to prostaglandins, essential fatty acids (EFAs) have now long been recognized as a factor in the treatment of many health related conditions. Prostaglandins are eicosanoids, which are short-lived, potent, locally acting cellular mediators that produce a broad range of biological affects on a multitude of tissues.

Prostaglandins (PGs) exist in virtually every mammalian tissue, acting as local hormones; they have important physiologic activities. A related series of compounds exist as well, the thromboxanes. Three different fatty acids (FAs) give rise to three groups of eicosanoids characterized by the number of double bonds in the side chains, e.g., PG_1, PG_2, and PG3. Different groups attach a ring structure in the compound that give rise to series of prostaglandins and thromboxanes, labelled A, B, etc. The leukotrienes and lipoxins are a third group of eicosanoid derivatives.

What is an Essential Fatty Acid?

Essential fatty acids are given that designation not because of the role they have in health but because the human body cannot make them. All fatty acids can be used by the body, but only two are considered essential and both are polyunsaturated fatty acids (PUFA): the omega-6 fatty acid, linoleic acid and the omega-3 fatty acid, alpha linolenic acid. All other fatty acids can theoretically, if all conditions are correct, be made from these 2 oils. EFA's have been used and researched for the treatment of cardiovascular disease (CVD), brain health and cognition including autism, some autoimmune conditions and cancer. While EFA's are needed by the body, research has shown some fatty acids are better than others when it comes to therapeutic efficacy.

Fatty acids refer to long chains of hydrocarbons that were once, or can be, a part of the larger molecule known as triacylglyerol (a fat molecule), that normally has 3 fatty acids in it. The naming of omega fatty acids indicates where the first carbon to carbon double bond occurs, for instance, in omega-9 it occurs at the number 9 carbon, in omega-3 it is at the third carbon atom from the methyl end of the molecule. The double bond is what makes the FA unsaturated. Monounsaturated fatty acids (MUFAs) that have one double bond, at the carbon #9, are called omega-9 oils. Olive oil is very high in the omega-9 oil, oleic acid; avocados are as well. Mediterranean diets are high in omega-9 oils, and it has been speculated that these oils in the diet are protective against heart disease based on the lifespan and expectancy of the people of that region. However, as omega-9 oils are not essential, and most diets have more than enough of them, there is no need for additional supplementation.

Omega-6 Fatty Acids and Metabolites

Omega-6 fatty acids are found in plant-based oils, and are considered polyunsaturated

fatty acids (PUFAs) because they contain more than one double bond. They are naturally occurring constituents present in sunflower, safflower, corn and soybean oils, walnuts, almonds, sesame seeds, pumpkin seeds and pine nuts. Linoleic acid (LA) is the primary EFA in this group, an 18 carbon long compound. It is prevalent in the standard diet, especially if you eat anything cooked with these oils or eat nuts. LA has little therapeutic value in of itself, but its metabolite, gamma-linoleic acid (GLA) has a stronger effect and is found in certain seeds such as evening primrose, borage and black current. GLA is converted, via an enzyme known as cyclooxygenase, to a prostaglandin of the E series, PGE1. This compound has a direct effect on the reduction of platelet aggregation and contributes to vasodilation, which can benefit those with heart disease. In addition it can also enhance cellular receptors to insulin, which can reduce problems associated with Type II diabetes and insulin resistance syndrome.

Since many people have high amounts of these oils in the diet already through the use of cooking oils, most supplementation is not needed. Our body converts LA to GLA via a desaturase enzyme which makes the molecule longer. This enzyme works as long as it has the proper nutrition and enzyme cofactors: vitamin B3, B6, and the minerals magnesium and zinc.

Arachidonic Acid: How it Creates Disease

However, the natural and more likely chemical conversion of dietary LA will go on to be converted into Arachidonic acid, a 20 carbon long chain fatty acid that is also found in animal products, specifically red meat, dairy and eggs. Arachidonic acid (AA) will lead to PG2 series of chemical mediators, which are pro-inflammatory, contribute to platelet aggregation and increased constriction of the vessels. The platelet aggregation and vessels changes if also coupled with a poor diet- which would favour low nutrients and high blood lipids- can contribute to an increased CVD risk. AA can also create thromboxanes of the 2 series, specifically thromboxane A2 (TXA2) which is a more potent vasoconstrictor and promotes platelet aggregation. In addition, eicosanoid metabolites from AA such as prostaglandin E2 (PGE2), leukotriene B4, 12-hydroxyeicosatetraenoic acid and TXA2 have all been positively linked to carcinogenesis.

The main pathway for AA into PGs is via a cyclooxygenase enzyme pathway, of which (COX) there are at least 2 different enzymes. COX enzymes always give rise to PG or Thromboxanes (TX) compounds. Some medications can block the activity of these enzymes. Several actually target them (commonly known as COX inhibitors). Some examples are Celebrex, Arcoxia and Mobic. These medications are primarily used for their anti-inflammatory nature. Other medications that actively inhibit COX enzymes are NSAIDS such as aspirin, ibuprofen, indomethacin; and some glucocorticoids like dexamethasone. But the COX enzymes are also needed to make other PG of the series 3 class, which are in of themselves anti-inflammatory. Blocking this enzyme with medication eliminates some of the other beneficial effects the PG3s have; anti-inflammatory, anti-thrombotic, anti-spasmodic and anti-cancer. For the temporary benefit of the anti-inflammation that these medications can give, an individual may be putting

themselves at risk for cancer and other chronic disease. But other fatty acids such as omega-3s can change that risk.

Omega-3 Fatty Acids: Which is the True Essential Fatty Acid?

Omega-3 fatty acids are more than just plant based oils, they are found in abundance in fish and marine products as well as some in seeds like flax, pumpkin and walnut. These are most commonly deficient fatty acids for people consuming a standard Western diet, which includes not only more red meat products but also a significant amount of processed foods. The EFA of the omega-3 class is alpha linoleinc acid (ALA), similar to LA but with 3 carbon to carbon double bonds. The other FAs of this class that are popular in clinical research are eicoapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

ALA has been touted as the primary EFA for dietary supplementation. Studies using ALA show a positive effect on lipid profiles, and it is beneficial in the treatment of CVD, as well as cancer. However, in humans there are no unique functions of ALA, other than as the precursor for EPA and DHA. In some animals ALA is used primarily in skin and hair.

Flaxseed oil is the most common form of supplementation of ALA. It contains approximately 53% ALA, but also 20% of an omega-9 monounsaturated fatty acid eicosenoic acid (which can also be made from oleic acid), and also 15% of omega 6 fatty acid, linolenic acid, with some of the remaining as saturated fatty acids. High amounts of flaxseed oil in the diet can therefore increase total fat intake considerably. Plus the conversions of ALA to EPA and DHA have been under scrutiny by clinicians and researchers. It is estimated that for every 1 gram of flaxseed oil ingested, only 0.02-6% can be made into EPA and even less, if any, DHA. Given the benefits associated with EPA and DHA, this is not enough for optimal health.

Therapeutic Effects of EPA: Protecting against Heart Disease and Cancer

EPA has the effect of slowing down the production of inflammatory chemicals that result from the arachidonic acid lines. EPA acts as a substrate for the COX enzyme reactions to make anti-inflammatory compounds, and also partially replaces AA in membrane lipids. This replacement allows for more fluidity to the cell.

Specifically, EPA leads to eicosanoids from the series 3 class, PGH3, PGI3 and TXB3. As mentioned above these compounds are anti-inflammatory, anti-thrombotic and anti-spasmodic. In addition, the PG3 class have anti mutagenic nature and discourage tumour cell proliferation. PGE3 from EPA has been shown to be an antagonist to PGE2 from AA in human lung cancer cells. PGE3 also reduces the activity of aromatase, an enzyme that contributes to elevated oestrogen metabolism and has a direct role in oestrogen mediated cancers. EPA, as well as its metabolite which is also present in fish oils- DHA- also reduces the risk of cancer by suppressing free radical reactive nitrogen species, reactive oxygen species, and free radicals which are implicated in tumour progression and also play a role in atherosclerosis.

Therapeutic Effects of DHA: a Key Nutrient in the Central Nervous System

DHA is the most highly unsaturated fatty acid found in cell membranes. It is found in the highest concentration in the membranes of nerve cells, in the retina and plays a key role in brain development. DHA is normally made from EPA when there is enough in the diet- or it is hypothesized that it is made via beta oxidation in cells. Since DHA has 6 carbon to carbon double bonds, it is considered to be 'superunsaturated'. This allows for even more cell membrane fluidity allowing for more uninhibited reactivity and regulation for cell functions, which is a highly advantageous milieu for the central nervous system and neurotransmitters. DHA is commonly found in a larger compound, phosphatidylserine, in the brain. In this aspect DHA may affect neuronal membranes, cell metabolism, and specific neuro-transmitter systems, including acetylcholine, noradrenaline, serotonin, and dopamine. These compounds can exert significant benefit on cognition, especially those functions which tend to decline with age- including memory, learning, vocabulary skills and concentration. As DHA plays an important role in the development of growing neural tissues, mothers who supplemented during pregnancy had infants that showed higher mental processing scores, psychomotor development and eye-hand coordination at 4 years of age. When given to school children, DHA has shown to play a beneficial role in enhancing learning capacity and academic performance. These factors also point to a role for DHA in autism and other neurological disorders. There is also evidence to suggest that depletion of DHA may be involved in postpartum depression, which is another reason why it should be recommended that all pregnant women, or women who are trying to get pregnant, supplement with DHA.

Is Fish Oil Supplementation then the Answer ?

If we follow the rationale that EPA and DHA are not essential because they both can be made from ALA, supplementation or dietary modifications are not necessary for some people: vegetarians who consume ample amounts of nuts and anyone who consume flaxseeds or oil. But it has been noted that the conversion from flaxseed oil makes only a fraction of EPA and perhaps no DHA. The first conversion of ALA to the next FA requires the enzyme delta-6-desaturase that can be affected in many ways. Desaturase enzymes need specific nutrients and enzyme cofactors: vitamin B3, B6, and minerals magnesium and zinc. Low amounts or deficiencies of those nutrients inactivate the enzyme. An elevated alcohol intake, trans-fatty acids, and saturated fats can all inhibit delta-6-desaturase. Also responsible for lowered enzymatic activity are the viruses HIV and Epstein-Barr virus (EBV), of which EBV causes infectious mononucleosis and has been implicated in patients with Chronic Fatigue Syndrome. Excess insulin, a factor in Type II Diabetes and Insulin Resistance Syndrome can also inhibit the enzyme pathway. A higher intake of omega 6- oils also inhibits the conversion of ALA to EPA by competing for the same delta- 6-desaturase.

Theoretically, humans evolved on a diet consisting of a 1:1 ratio of omega-6 to omega-3 fatty acids. Currently, the typical Western diet consists of omega-6: omega-3 ratios between 10:1 and 25:1 and in some cases may be as high as 40:1. Since omega-3 and

omega-6 FAs compete for the same enzyme, the high amounts of omega-6 FAs lead to elevated levels of AA in cell membranes. This imbalanced fatty acid ratio is one of the major underlying factors in chronic inflammatory health problems. The metabolites of AA can contribute to CVD and cancer, the two main killer diseases of our age. By manipulating the levels of AA, we can change our disease risk and over all decrease mortality. The best way to change dietary FA is by the addition of fish oils into the diet. It is important to consider the quality and cleanliness of the fish or fish oils consumed, in particular the mercury which is polluting the oceans and the fish. Also of importance are newer dangerous man-made chemicals like dioxins and polychlorinated biphenyls (PCBs) that also make it way into the fish bodies via the sea. By supplementing with clean, high quality fish oil we can increase health and wellness, clear thinking and awareness, not only for ourselves but for our children and future generations.

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