Functional Medicine University’s
Functional Diagnostic Medicine
Training Program

Module 5 * FMDT 541B

Inflammation and the Role of Essential Fatty Acids

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Contents

The Function of Fatty Acids ................................................................. 2
Cell Membrane Structure and Function .............................................. 3
Fatty Acid Structure and Metabolism ............................................... 4
Naming Conventions for Unsaturated Fatty Acids .............................. 5
Hepatocyte Regulation of Blood Lipids .............................................. 6
Elongation and Desaturation of Fatty Acids ....................................... 7
Microsomal Conversion of Linoleic to Arachidonic Acid ....................... 7
Metabolism of Omega 3 and Omega 6 Fatty Acids .............................. 8
Metabolism of Omega 6 Fatty Acids ................................................ 8
  Eicosanoids – The Mediators Involved in the Inflammatory Process ........ 9
Essential Fatty acids and Cardiovascular Health ................................ 19
In Summary .................................................................................. 19
References .................................................................................... 20

Required Reading: Latest Findings on Essential Fatty Acids and Cardiovascular Health: The Original Internist, June 2008 (Located with this lesson on www.FunctionalMedicineUniversity.com.)
The Function Fatty Acids

“Fish oil may be inversely associated with breast cancer risk”\(^1\). That was the conclusion in a recent 2010 report in *Cancer Epidemiology, Biomarkers & Prevention* a journal of the American Association for Cancer Research. The research was conducted at the Fred Hutchinson Research Center in Seattle, Washington. Over 35,000 postmenopausal women, who did not have a history of breast cancer, were asked to fill out a questionnaire about their non-vitamin and non-mineral supplement use. A six years follow-up identified 880 cases of breast cancer using the Surveillance, Epidemiology and End Results registry (SEER). The SEER program of the National Cancer Institute is an authoritative source of information on cancer incidence and survival in the United States. The results of the study concluded that supplementation with EPA and DHA was linked with a 32 percent reduced risk of invasive ductal breast cancer, the most common type of the disease.

Fatty Acids

Essential fatty acids are fats that the body is unable to make on its own. They must be ingested by consuming plants or eating animals that consume plants. Fatty acids are needed to maintain cell membrane integrity and chemical transport that is involved in proper development of the central nervous system, energy production, cell communication, oxygen transport, and regulation of inflammation\(^2\). Essential fatty acids are components of the cell membrane and therefore determine cell membrane fluidity, hormone binding, cell receptor activity, membrane bound enzyme activity and transport channel function. Essential fatty acids are also precursors of eicosanoids, which are the messengers involved with the inflammatory process.

Long term restriction of essential fatty acid, as well as excess animal fats, have been strongly correlated to several disease conditions, including chronic disease. Fatty acid levels are determined primarily by dietary intake and genetics, though estrogen levels and parity are factors that contribute to essential fatty acid status among women, and variations in testosterone levels have a significant influence on fatty acid status in men\(^3\). Estrogens appear to upregulate synthesis of DHA and testosterone is involved in polyunsaturated fatty acid biosynthesis, and modulating delta-5 and delta-6 desaturase activity\(^4, 5\). Dietary intake of fat, insufficient or excess, has been related to several forms of cancer; however this relationship may be complicated by nutritional status and genetic factors\(^3\). In recent years a new hypothesis has been proposed in regard to the development of cancer and altered cell membrane essential fatty acids\(^6\). This hypothesis theorizes that altered essential fatty acid composition in the cell membrane reduces the transport of oxygen into the cells and therefore increases the risk of cancer.

It is interesting to note that low fasting serum triglyceride level can serve as a precocious marker of autoimmune disease and immune system hyperactivity\(^7\). (You should recall that triglycerides are composed of a glycerol and three fatty acids.) Decreased triglyceride level was observed in patients with lupus, scleroderma, urticaria, Reiter syndrome, Sjogen syndrome, rheumatoid arthritis, ulcerative colitis, Crohn’s disease, and multiple sclerosis\(^7\). You should consider an autoimmune process if you observe a low triglyceride level with low to normal cholesterol and a high HDL on your blood test results, along with other clinical considerations.
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Essential Fatty Acids and the Nervous System

Essential fatty acid deficiency can contribute significantly to nervous system dysfunction due to the fact that there is a high fat content in the nervous system which is important for nerve signaling. Oxidation of neuronal membrane polyunsaturated fatty acids can cause damage to the nervous system leading to neurodegeneration. Membrane fatty acid composition affects the function of neurons by changing membrane fluidity and function, by altering local signaling, by means of eicosanoid/docosanoid synthesis, or by altering gene expression/transcription by means of peroxisome proliferator-activated receptors (PPARs).³

Cell Membrane Structure and Function

All membranes contain lipid and protein; however the proportion of each varies depending on the particular membrane. For example, the mitochondrial inner membrane contains 76 percent protein and 24 percent lipid as opposed to the myelin in the nerve fibers, which contain 18 percent protein and 76 percent lipid.

The dominant form of fatty acid is phospholipid. Phospholipids have a polar head and two fatty acid (hydrocarbon) tails. These compounds are collectively known as phosphotides. They are the basic structural component of the cell membranes. A membrane bound enzyme called phospholipase is responsible for the ever change membrane composition. A form of the enzyme called PLA2 (phospholipase A2) is involved with the injury/inflammatory response. This enzyme, of which there are more than 19 isoforms, is involved with the release of arachidonic acid from the cell membrane and synthesis of eicosanoids.

The cell membrane is made up of a lipid bilayer in which the polar heads are on the outside and the non-polar hydrocarbon portion is on the inside. Cholesterol is also incorporated into the cell membrane. Cholesterol has a rigid ring system and a short branched hydrocarbon tail. Cholesterol prevents crystallization of the hydrocarbons and prevents phase shift in the membrane. Some have referred to membrane cholesterol as acting like “antifreeze”; in cold weather it keeps the membrane fluid; and in hot weather, it keeps the membrane rigid. Other constituents of the membrane include; protein, glycoprotein and glycolipids. Phosphatidylcholine, a glycerophospholipid, is also a common membrane lipid.
Fatty Acid Structure and Metabolism

There are about forty physiologically significant fatty acids, not including derivatives such as hydroxyl- and branched fatty acids. The key structural features of fatty acids are; the number of carbon atoms, the number of double bonds and the location of the double bonds. Slight structural differences of fatty acids can cause profound effects on cellular function. It is known that trans-fatty acids are more atherogenic than saturated fatty acid, and that trans-fatty acids alter the expression of different genes associated with insulin sensitivity in adipose tissue.
Naming Conventions for Unsaturated Fatty Acids

Fatty acids are usually not found in the free form in nature, but occur in the esterified form as the major component of lipid. Dietary sources of fatty acids include triglycerides, in solid or liquid form, and from phosphotides in whole foods. Because of their critical role life-support function in forming cell membranes and supplying energy sources and hormone controls, there are mechanisms for assuring that the supply of fatty acids will be continuous, even during short intervals between meals.
Hepatocyte Regulation of Blood Lipids

Elongation and Desaturation of Fatty Acids

Desaturation reactions add double bonds to the fatty acid and elongation reactions add two carbons to the carboxyl end. These reactions are performed by the enzymes, elongase and desaturase. As stated earlier, essential fatty acids must be consumed because they cannot be manufactured by the body. Consumption of the two primary or “parent” forms of EFA’s allow the body to synthesize whatever EFA “derivatives” it needs from them. This synthesis is performed by the enzymatic activity of elongase and desaturase. These two primary forms are parent omega-6, linoleic acid (LA) and parent omega-3, termed alpha-linolenic acid (ALA) \(^6\). Thus, in the strictest sense, EFA’s are only LA and ALA. Linoleic acid has 18 carbons and two double bonds at the 6\(^{th}\) and 9\(^{th}\) carbon from the methyl side of the molecule (18:2n6). Alpha-linolenic acid has 18 carbon and three double bonds at the 3\(^{rd}\), 6\(^{th}\), and 9\(^{th}\) carbon from the methyl side of the molecule (18:3n3). The activity of the desaturase enzymes are critical for maintaining the ratio of saturated to unsaturated components of the cell membranes \(^3\). The enzyme called delta-6-desaturase is noteworthy. Delta-6 desaturase is the first enzyme used to synthesis the other fatty acid from the “parent” fatty acid. Delta-6 desaturase is a zinc dependent enzyme; therefore, a zinc deficiency will decrease the rate of synthesis. The activity of delta-6 desaturase is also inhibited by the following: magnesium deficiency, elevated serum insulin, and high concentrations of saturated, monosaturated and trans-fatty acid.

Microsomal Conversion of Linoleic to Arachidonic Acid

Metabolism of Omega 3 Fatty Acids

Omega 3 Fatty Acids

Alpha Linolenic Acid (ALA)
18:3n-3
Essential Fatty Acid

Delta-6 Desaturase

Stearidonic Acid
18:4n3

Elongase

n-3 Eicosatetraenoic Acid
20:4n3

*Delta-5 Desaturase

Eicosapentaenoic Acid (EPA)
20:5n-3

Stimulated by:
Cyclooxygenase Enzyme Complex

Prostaglandin E3 (PGE3)

DOCSAHEXAENOIC ACID (DHA)
22:6n-3

Needed for healthy brain development

Metabolism of Omega 6 Fatty Acids

Omega 6 Fatty Acids

LINOLEIC ACID (LA)
18:2n-6

Delta-6 Desaturase

Evening Primrose Oil

GAMMA LINOLENIC ACID (GLA)
18:3n-6

Stimulated by:
B6 & Magnesium

DIHOMO GAMMA LINOLENIC ACID (DGLA)
20:3n-6

Stimulated by:
Cyclooxygenase Enzyme Complex

Prostaglandin E1 (PGE1)

Inhibited by:
NSAIDS & Aspirin

Stimulated by:
Cyclooxygenase Enzyme Complex

Prostaglandin E2 (PGE2)

Inhibited by:
NSAIDS & Aspirin
Quercetin
Vit E & EPA

Leukotrienes

Red Meats, Dairy Fats, Shellfish
Causes of EFA Imbalances Leading to Inflammation

1. Biochemical uniqueness
2. Low Delta-6 desaturase activity due to micronutrient deficiencies (B6, Biotin, Vitamin C, Zn, Mg)
3. Insulin dysregulation
4. Standard American/Western Diet

Eicosanoids – The Mediators Involved in the Inflammatory Process

The eicosanoids, which literally means twenty carbons, are synthesized through the cascade of reactions involving desaturation and elongation of the essential fatty acids. The overall function of the desaturation and elongation sequence is to maintain levels of DGLA, AA and EPA for incorporation into the biological membranes. These three polyunsaturated fatty acids are the parent compounds of the series 1, series 2 and series 3 prostanoids (prostaglandin and thromboxane) and leukotriene pathways.3

Introduction to the Eicosanoids*

The eicosanoids consist of the prostaglandins (PG), thromboxanes (TX), leukotrienes (LT) and lipoxins (LX). The PGs and TXs are collectively identified as prostanoids. The nomenclature of the prostanoids includes a subscript number which refers to the number of carbon-carbon double bonds that exist in the molecule. The majority of the biologically active prostaglandins and thromboxanes are referred to as series 2 molecules due to the presence of two double bonds. The predominant leukotrienes are series 4 molecules due to the presence of four double bonds. There are, however, important series 1 prostaglandins and thromboxanes as described below.

Prostaglandins were originally shown to be synthesized in the prostate gland, thromboxanes from platelets (thrombocytes) and leukotrienes from leukocytes, hence the derivation of their names. The lipoxins are anti-inflammatory eicosanoids synthesized through lipoxygenase interactions (hence the derivation of the name).
The eicosanoids produce a wide range of biological effects on inflammatory responses (predominantly those of the joints, skin and eyes), on the intensity and duration of pain and fever, and on reproductive function (including the induction of labor). They also play important roles in inhibiting gastric acid secretion, regulating blood pressure through vasodilation or constriction, and inhibiting or activating platelet aggregation and thrombosis.

The principal eicosanoids of biological significance to humans are a group of molecules derived from the C20 fatty acid, arachidonic acid. Additional biologically significant eicosanoids are derived from dihomo-γ-linolenic acid (DGLA) which is produced in the reaction pathway leading to arachidonic acid from linoleic acid. Minor eicosanoids are derived from eicosapentaenoic acid which is itself derived from α-linolenic acid or obtained in the diet. The major source of arachidonic acid is through its release from cellular stores. Within the cell, it resides predominantly at the C–2 position of membrane phospholipids and is released from there upon the activation of PLA2.

The immediate dietary precursor of arachidonate is linoleic acid. Linoleic acid is converted to arachidonic acid. The activity of the Δ6-desaturase is slow and can be further compromised due to nutritional deficiencies as well as during inflammatory conditions. Therefore, maximal capacity for synthesis of arachidonic acid occurs with ingested γ-linolenic acid (GLA) the product of the Δ6-desaturase. GLA is converted to dihomo-γ-linolenic acid (DGLA) and then to arachidonic acid. Like the Δ6-desaturase, the activity of the Δ5-desaturase is limiting in arachidonic acid synthesis and its activity is also influenced by diet and environmental factors. Due to the limited activity of the Δ5-desaturase most of the DGLA formed from GLA is inserted into membrane phospholipids at the same C-2 position as for arachidonic acid.

Metabolism of the Eicosanoids

All mammalian cells except erythrocytes synthesize eicosanoids. These molecules are extremely potent, able to cause profound physiological effects at very dilute concentrations. All eicosanoids function locally at the site of synthesis, through receptor-mediated G-protein linked signaling pathways.

Two main pathways are involved in the biosynthesis of eicosanoids. The prostaglandins and thromboxanes are synthesized by the cyclic pathway, the leukotrienes by the linear pathway.

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Eicosanoids from Cell Membrane Fatty Acids

Numerous stimuli (e.g. epinephrine, thrombin and bradykinin) activate PLA₂ which hydrolyzes arachidonic acid from membrane phospholipids. The prostaglandins are identified as PG and the thromboxanes as TX. Prostaglandin PGI₂ is also known as prostacyclin. PGE₂ is synthesized from PGH₂ via the action of one of several PGE synthases, where PGE synthase-1 (PGES1) appears to be the key enzyme. Two forms of PGD₂ synthases have been identified (hematopoietic and lipocalin prostaglandin D synthases, hPGDS and lPGDS) that convert PGD₂ from PGH₂. Prostacyclin (PGI₂) is synthesized from PGH₂ via the action of prostacyclin synthase (PGIS). Prostaglandin F synthase (PGFS) converts PGH₂ to PGF₂α or PGD₂ to 9α,11β-PGF₂α,β.
Synthesis of the Clinically Relevant Leukotrienes from Arachidonic Acid*

The leukotrienes are identified as LT. Numerous stimuli (e.g. epinephrine, thrombin and bradykinin) activate PLA₂ which hydrolyzes arachidonic acid from membrane phospholipids. The enzyme 5-lipoxygenase (5-LOX) in association with the protein, 5-LOX activating protein (FLAP), catalyzes the conversion of arachidonic acid, first to 5-hydroperoxyeicosatetraenoic acid (5-HPETE) which spontaneously reduces to 5-hydroxyeicosatetraenoic acid (5-HETE), and then to LTA₄. LTA₄ is unstable and is converted to LTB₄ in neutrophils and monocytes harboring LTA₄ hydrolase. In mast cells and eosinophils, which harbor LTC₄ synthase, LTA₄ is converted to LTC₄. The leukotrienes LTC₄, LTD₄, LTE₄ and LTF₄ are known as the peptidoleukotrienes or the cysteinyl leukotrienes because of the presence of amino acids. The peptidoleukotrienes, LTC₄, LTD₄ and LTE₄ are components of slow-reacting substance of anaphylaxis (SRSA). SRSA was originally identified as an activity released from sensitized lung after immunologic challenge. The subscript 4 in each molecule refers to the number of carbon-carbon double bonds present.

Synthesis of the lipoxins from arachidonic acid via transcellular interactions. Three pathways exist for the synthesis of the lipoxins. The "classic" pathway involves 5-LOX activity in leukocytes followed by 12-LOX action in platelets. The action of 15-LOX in epithelial cell (such as in the airway) followed by 5-LOX action in leukocytes is the second major lipoxin synthesis pathway. The linear pathway is initiated through the action of lipoygenases (LOXs) of which there are three forms, 5-LOX, 12-LOX and 15-LOX. It is 5-LOX that gives rise to the leukotrienes. The leukotrienes are synthesized by several different cell types including white blood cells (leukocytes, hence the derivation of the name of the compounds), mast cells, lung, spleen, brain and heart.

The lipoxins are synthesized through the concerted actions of 15-LOX (acting on arachidonic acid in epithelial cells, such as in the airway) followed by 5-LOX in leukocytes or through the actions of 5-LOX in leukocytes followed by 12-LOX action in platelets.

The cyclic pathway is initiated through the action of prostaglandin G/H synthase, PGS (also called prostaglandin endoperoxide synthetase). This enzyme possesses two activities, cyclooxygenase (COX) and peroxidase. There are 3 forms of the COX activity. COX-1 (PGS-1) is expressed constitutively in gastric mucosa, kidney, platelets, and vascular endothelial cells. COX-2 (PGS-2) is inducible and is expressed in macrophages and monocytes in response to inflammation. The primary triggers for COX-2 induction in monocytes and macrophages are platelet-activating factor, PAF and interleukin-1. Both COX-1 and COX-2 catalyze the 2-step conversion of arachidonic acid to PGG₂ and then to PGH₂.

The major dietary sources of GLA are borage oil, evening primrose seed oil, hemp seed oil, and black currant seed oil. Diets containing sources of GLA have been shown have distinct cardiovascular benefit similar to diets rich in omega-3 polyunsaturated fatty acids such as is found in cold water fishes.

Eicosanoids and Inflammatory Responses*

Each of the eicosanoids function via interactions with cell-surface receptors that are members of the G-protein coupled receptor (GPCR) family. There are at least 9 characterized prostaglandin receptors. Receptors that bind the prostaglandin D family of lipids are called the PGD receptors and those that bind E family prostaglandins are called the PGE receptors. The PGD receptors are coupled to the production of cAMP and activation of PKA.
The PGE receptors couple to the activation of PLCγ and as a consequence the production of DAG and IP₃ from membrane phospholipids. The receptor for prostacyclin (PGI₂) is called the PC receptor and it couples to production of cAMP. There are 2 receptors that bind LTB₄ called BLT₁ and BLT₂. The peptidoleukotrienes (cysteinyl leukotrienes) bind to receptors called CysLT1 and CysLT2. The thromboxane receptor is coupled to the activation of PLCγ.

As indicated in the Table below, the major actions of the series-2 prostaglandins and thromboxanes (predominantly PGE₂ and TXA₂) are pro-inflammatory as are the series-4 leukotrienes (predominantly LTB₄).

Research over the past 10–15 years has demonstrated the physiological benefits (i.e. anti-inflammatory) of alternative pathways of polyunsaturated fatty acid metabolism. As described above for the synthesis of, much of the DGLA derived from ingested linoleic acid or GLA is diverted into membrane phospholipids due to the inefficiency of the Δ⁵-desaturase catalyzing the conversion of DGLA to arachidonic acid. Incorporation of DGLA into membrane phospholipids competes with the incorporation of so that diets enriched in GLA result in an alteration in the ratio of membrane to DGLA. Release of membrane DGLA occurs through the action of PLA₂ just as for release of. Once DGLA is released it will compete with for COXs and LOXs. The products of COX action on DGLA are series-1 prostaglandins (PGE₁) and thromboxanes (TXA₁). These eicosanoids are structurally similar to the series-2 eicosanoids except, of course, they have a single double bond. Although structurally similar, the series-1 eicosanoids have distinctly different biological actions. PGE₁ and TXA₁ are anti-inflammatory, they induce vasodilation, and they inhibit platelet aggregation. When DGLA is a substrate for 15-LOX the product is 15-hydroxyeicosatrienoic acid (15-HETrE). 15-HETrE is a potent inhibitor of 5-LOX which is the enzyme responsible for the conversion of arachidonic acid to LTB₄. LTB₄ is a potent inflammatory molecule through its action on neutrophils, thus, DGLA serves to inhibit inflammation via the linear eicosanoid pathway as well.
<table>
<thead>
<tr>
<th>Eicosanoid</th>
<th>Major site(s) of synthesis</th>
<th>Major biological activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>LXA₄</td>
<td>platelets, endothelial cells, mucosal epithelial cells and other leukocytes via interactions with PMNs</td>
<td>reduce PMN and eosinophil infiltration to sites of inflammation, stimulate nonphlogistic (non-inflammatory-inducing) monocyte recruitment, stimulate macrophage phagocytosis of apoptotic PMNs, block IL-8 (chemokine) expression, block TNF-α release and actions, stimulate TGF-β action</td>
</tr>
<tr>
<td>LXB₄</td>
<td>platelets, endothelial cells, mucosal epithelial cells and other leukocytes via interactions with PMNs</td>
<td>same as for LXA₄</td>
</tr>
<tr>
<td>PGD₂</td>
<td>mast cells</td>
<td>inhibits platelet and leukocyte aggregation, decreases T-cell proliferation and lymphocyte migration and secretion of IL-1α and IL-2; induces vasodilation and production of cAMP</td>
</tr>
<tr>
<td>PGE₁</td>
<td></td>
<td>induces vasodilation and inhibits platelet aggregation</td>
</tr>
<tr>
<td>PGE₂</td>
<td>kidney, spleen, heart</td>
<td>increases vasodilation and cAMP production, enhancement of the effects of bradykinin and histamine, induction of uterine contractions and of platelet aggregation, maintaining the open passageway of the fetal ductus arteriosus; decreases T-cell proliferation and lymphocyte migration and secretion of IL-1α and IL-2</td>
</tr>
<tr>
<td>PGF₂α</td>
<td>kidney, spleen, heart</td>
<td>increases vasoconstriction, bronchoconstriction and smooth muscle contraction</td>
</tr>
<tr>
<td>PGH₂</td>
<td></td>
<td>precursor to thromboxanes A₂ and B₂, induction of platelet aggregation and vasoconstriction</td>
</tr>
<tr>
<td>PGI₂</td>
<td>heart, vascular endothelial cells</td>
<td>inhibits platelet and leukocyte aggregation, decreases T-cell proliferation and lymphocyte migration and secretion of IL-1α and IL-2; induces vasodilation and production of cAMP</td>
</tr>
<tr>
<td>TXA₁</td>
<td></td>
<td>induces vasodilation and inhibits platelet aggregation</td>
</tr>
<tr>
<td>TXA₂</td>
<td>platelets</td>
<td>induces platelet aggregation, vasoconstriction, lymphocyte proliferation and bronchoconstriction</td>
</tr>
<tr>
<td>TXB₂</td>
<td>platelets</td>
<td>induces vasoconstriction</td>
</tr>
<tr>
<td>LTB₄</td>
<td>monocytes, basophils, neutrophils, eosinophils, mast cells, epithelial cells</td>
<td>powerful inducer of leukocyte chemotaxis and aggregation, vascular permeability, T-cell proliferation and secretion of INF-γ, IL-1 and IL-2</td>
</tr>
<tr>
<td>LTC₄</td>
<td>monocytes and alveolar macrophages, basophils, eosinophils, mast cells, epithelial cells</td>
<td>component of SRS-A, microvascular vasoconstrictor, vascular permeability and bronchoconstriction and secretion of INF-γ, recruitment of leukocytes to sites of inflammation, enhance mucus secretions in gut and airway</td>
</tr>
<tr>
<td>LTD₄</td>
<td>monocytes and alveolar macrophages, eosinophils, mast cells, epithelial cells</td>
<td>same as LTC₄</td>
</tr>
<tr>
<td>LTE₄</td>
<td>mast cells and basophils</td>
<td>same as LTC₄</td>
</tr>
</tbody>
</table>

**SRS-A = slow-reactive substance of anaphylaxis

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Lipoxygenase and Cyclooxygenase Enzyme Products

Metabolism of Omega-3 fatty acids

Alpha-linolenic acid
ALA 18:3n3
‘essential fatty acid’

Delta-6-desaturase
Very slow rate limiting conversion
Requires: Zn, Mg, pyridoxine, iron
Facilitated by: vitamin C
Inhibited by: EPA, DHA, catecholamines

Stearidonic Acid 18:4n3

Eicosanoids
3-series prostaglandins and thromboxanes
General actions: lower blood pressure, prevent clots, block formation of 2-series PGs (which raise blood pressure, promote clots, etc) from omega-6

Cyclooxygenase
Inhibited by ginger, aspirin, DHA

Liberation from phospholipids by phospholipase-A2

5-series leukotrienes

Anti-inflammatory, antiproliferative, and anticarcinogenic; suppression of NF-kappaB

Eicosapentaenoic acid EPA 20:5n3
Fatty fish, fish oil, cod liver oil

Delta-5-desaturase

n-3 docosapentaenoic acid
N-3 DPA 22:5n3

Delta-4-desaturase

Docosahexaenoic acid
DHA 22:6n3
Fatty fish, fish oil, cod liver oil, microalgae

Anti-inflammatory, antiproliferative anticarcinogenic

Appears to downregulate inflammation (CRP, IL-6) and prostaglandin production
Metabolism of Omega-6 fatty acids

Linoleic Acid
LA 18:2n-6

Delta-6 desaturase
Impaired with deficiency of: Zn, Mg, pyridoxine, iron, ascorbate, niacin, and riboflavin. Inhibited by: EPA, DHA, catecholamines

Prostaglandin E-1: PGE-1
Anti-inflammatory, vasodilation, inhibits platelet aggregation

Cyclooxygenase
Inhibited by ginger, turmeric, holy basil, NSAIDs

Gamma-linolenic acid
GLA 18:3n-6
Evening primrose oil, borage seed oil, hemp oil, black current seed oil, vitamin C increases GLA production from LA: EPA inhibits GLA formation

Phospholipase A2

Delta-5-desaturase
Activates NF-kappaB; increases superoxide generation; impairs several pathways of cytochrome P450 detoxification

Arachidonic acid
ARA 20:4n6

Liberation from phospholipids by phospholipase A2

Cyclooxygenase
Inhibited by: NSAIDs, ginger, turmeric, EPA, gamma-tocopherol

Adrenic acid
22:4n-6

N-6 docosapentaenoic acid
22:6n-6

PG12 (prostacyclin):
produced by COX-2;
decreases platelet aggregation; lowers blood pressure; increases pain

Prostaglandin E2 (PG-E2):
promotes inflammation, chemotaxis, edema; sensitizes neurons to increased duration and intensity of pain perception; induces fever in the hypothalamus, protects gastric mucosa, reduces apoptosis and promotes cancer, induces COX, increases IgE production; upregulates aromatase, increased by nitric oxide

PG-F2a:
increases uterine contractions, increased levels associated with dysmenorrhea, formation suppressed by vitamin C

Prostaglandin H2 (PG-H2):
Rapid platelet aggregation

Collagenases/matrix metalloproteinases facilitate joint destruction

5-HPETE
Promotes tissue destruction via lysozymes

5-HETE

PG-G2
Rapid platelet aggregation

5-lipoxygenase
Inhibited by boswellia

Dihomo gamma-linolenic acid
Breast milk

NF-kappaB
Essential Fatty acids and Cardiovascular Health

Dr. Mark Houston, a clinical professor of medicine at Vanderbilt University School of Medicine and the director of the Hypertension Institute and Vascular Biology at Saint Thomas Hospital in Tennessee, has conducted extensive research on the importance of the optimal proportion of essential fatty acids as it relates to cardiovascular health. Dr. Houston has outlined the optimal ratio of omega-3 to omega-6 fatty acids and vitamin E requirements. Vitamin E is important to protect the membranes from lipid peroxidation, which leads to oxidative stress. His recommended maintenance ratio is a 2:1 mixture of omega-3 to omega-6 (in the form of GLA) in addition to mixed tocopherols (gamma, delta and alpha). Dose considerations are critical when prescribing essential fatty acids. Low dosages have not been shown to be beneficial in the treatment of cardiovascular disease, rheumatoid arthritis, and psoriasis. If your patient has a chronic disease condition, I personally recommend ordering a RBC fatty acid analysis. This will enable to prescribe patient-specific dosage and achieve optimal outcomes.

Required Reading: Latest Findings on Essential Fatty Acids and Cardiovascular Health: The Original Internist, June 2008 (Located with this lesson on www.FunctionalMedicineUniversity.com.)

In Summary

Essential fatty acids have two important roles. The first is for membrane fluidity and the second is to act as precursor of eicosanoids, which are involved in the inflammatory process. The functional medicine practitioner must always search for the underlying cause of the dysfunction and not just prescribe a supplement or supplements for a particular disease.
References

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