

Feeling Swell: Inflammation

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Everyone has felt the redness, warmth, swelling, and pain of inflammation when we hit a finger with a hammer, twist an ankle or experience some other similarly unpleasant situation. These are all normal reactions of your body as it starts to repair the damaged body tissues. They are signs that the immune, circulatory and hormonal systems have begun to fix the injured tissues.

These next two articles explain our current understanding of inflammation. This first article is very complicated and some parts might be a challenge to read. Don't give up! We hope that people will be able to prevent diseases known to be related to chronic inflammation and to find ways to combat chronic inflammation if they understand the process. If this article proves too much to handle, the second article is much less technical and discusses prevention and treatment of chronic inflammation. You can still gain a lot from just reading and following the second article without understanding every detail in this article.

Inflammation is a topic of hot debate and extensive research. There are still many unanswered questions about the full potential of natural anti-inflammatories that have much fewer side effects than current medications, the benefit of treating acute inflammation, how the body synthesizes substances affecting chronic inflammation, and how changes in diet affect the process.

Inflammation is a process where white blood cells and plasma leave the blood vessel and go into the surrounding tissues where they release chemicals that protect the body from infection, bacteria and viruses.^{1,2} Inflammation actually serves a purpose. But it creates illness when it continues beyond normal limits.³ In some diseases, the body's immune system triggers an inflammatory response when there are no foreign substances to fight. The body responds as if normal tissues are infected. In this case, the immune system damages its own tissues. This is true in autoimmune diseases such as rheumatoid arthritis and lupus. Inflammation is also a major component of musculoskeletal disease (e.g., Repetitive Strain Injury), osteoarthritis, and tendinitis.^{2,3}

It is important to differentiate between "acute" inflammation that results from sudden traumatic injuries and "chronic" inflammation that is abnormal and goes on beyond the immediate response to sudden injury.¹ In the less severe cases, acute inflammation resolves itself within a few hours, or it could take a few days for the body to recover. If not, it develops into chronic inflammation or, in severe cases, it can take over the whole body and become fatal (sepsis).

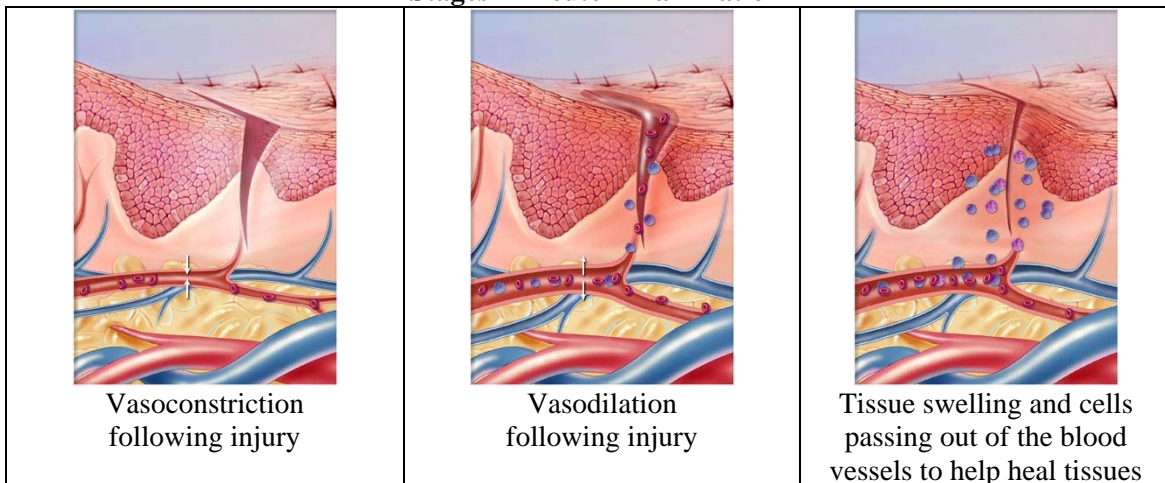
Acute Inflammation Process

Acute inflammation starts with a brief phase of arterial constriction followed by artery dilation that increases blood flow to the injured area.¹ The capillaries become more permeable and leak protein-rich plasma into the tissue. Blood flow then slows, allowing white blood cells called neutrophils to line up and stick to the cells of the damaged blood vessels and red cells to pack the small blood vessels.^{1,4} At the same time, the plasma-derived proteins undergo various changes that lead to the immune response and the formation of fibrin, a framework for eventual scar tissue.^{1,4}

The increased fluid in the tissue causes an increased flow of lymph which carries the immune complexes to the lymph nodes. When the neutrophils (white blood cells) arrive at the site of injury, they work to deactivate infection and kill dead tissue debris. This whole process is orchestrated by several chemical

mediators derived from the injured tissues, bacteria, plasma proteins, and leucocytes (other white blood cells).

Stages in Acute Inflammation



Illustrations courtesy of www.gluegrant.org, Reference 5

After the first phase of inflammation, as early as the second or third day of acute inflammation, macrophages (a different type of white blood cell) accumulate in increasing numbers.¹ These enter the tissue in a similar manner as the neutrophils in the first phase and they proceed to digest cell debris, dead neutrophils, and fibrin.¹

Treatment

We've all heard through doctors and sports medicine literature that we need to apply ice and compression as soon after injury as possible to avoid inflammation and to promote healing. But, if inflammation is a normal part of healing, why would we want to inhibit it? The argument for reducing inflammation is that healthy tissue is not inflamed, so if we stop inflammation in an injured tissue it will be healthier.⁶ However, there is not universal agreement that acute inflammation should be reduced or that it aids healing.

Local cooling has not been shown to be beneficial in preventing inflammation from injuries or burns, though it does appear to be effective in reducing pain, especially when used in conjunction with compression.^{7, 8} One study on rats found that the permeability of small blood vessels was significantly reduced following ice therapy in the treatment of muscle injuries.⁹ This effect actually inhibits healing since reducing the permeability restricts the release of protein into the damaged tissue.⁹

Use of ice has also been shown to reduce the temperature of bone and joints by several degrees in addition to superficial cooling of tissues.¹⁰ This causes cooling of the synovial fluids, which probably affects the growth rate of some proteins in the synovial fluid (cytokines).¹⁰ It has not been proven if this effect is beneficial.

With regard to the use of aspirin and non-steroidal anti-inflammatories (NSAIDs) to reduce acute inflammation, a recent review of studies on strains, contusions, and delayed-onset muscle soreness revealed minimal benefit of NSAIDs when compared with a placebo.⁶ Some literature suggests that NSAIDs may delay the rate of muscle fiber regeneration.⁶ Interestingly, the use of anabolic steroids has been shown to *increase* inflammation and simultaneously, hasten the healing of muscle injuries.⁶ In general, research is lacking to either prove or disprove NSAIDs effective in treating musculoskeletal injuries, but at best it appears that it is an effective pain reliever and as such, may facilitate the healing of ligament injuries by encouraging activity.⁶

Chronic Inflammation

Chronic inflammation is strongly suspected in many degenerative diseases, such as:^{5,11}

- Arthritis
- Repetitive Strain Injuries
- Alzheimer's and Parkinson's disease
- Cancer
- Heart disease
- Inflammatory bowel disease
- Asthma
- Inflammatory skin problems (e.g., eczema and psoriasis)
- Depression
- Bi-polar disorder
- Multiple sclerosis

When inflammation is relieved, or if it is prevented, incidence of these problems is reduced. Why the chronic inflammation exists and how it creates problems is not yet well understood.

Chronic inflammation is characterized by infiltration of the tissue with mononuclear inflammatory cells: monocytes, lymphocytes, and/or plasma cells.⁴ Good tissue is destroyed and scar tissue is often seen. Tissue destruction is caused both by the causative agent and by the inflammatory process itself.¹²

Plasma cells produce antibodies against a persistent antigen or altered tissue components. Lymphocytes are likely to be present even when there is no involvement of the immune system.⁴

In chronic inflammation, the feedback systems breakdown and the "bad" guys gain ground in the body's battle to control inflammation. For this reason, reduction of chronic inflammation is very important in the promotion of health.

Understanding Chronic Inflammation

What is known is that inflammation is not affected by age. Adequate blood supply and good nutrition is required for healing.⁴ The inflammatory response is inhibited by diabetes and glucocorticoids due to their interference with most whole blood cell functions.⁴ Stress increases the level of glucocorticoids that are synthesized by the body from cholesterol.¹³

Cytokines and Chronic Inflammation

There are two "bad" proteins called cytokines that are involved in the inflammation process and share many properties.

1) Interleukins (IL-1) are proteins secreted by the white blood cells to activate other cells. They coordinate and regulate various biological processes.¹⁴ IL-1 promotes production of prostaglandins, bone growth and the growth of white blood cells.^{14,15} High levels of IL-1 in the blood are associated with many inflammatory conditions. In addition, it appears that IL-1 is a potent activator of fibroblasts (precursor of connective tissue) and probably accounts for the scarring in chronic inflammatory diseases.⁴

2) Tumor Necrosis Factor (TNF) stimulates IL-1 and increases the tissue damaged by IL-1.¹⁴

Preliminary research has shown that blocking TNF reduces IL-1 and appears to be effective in combating chronic inflammation in rheumatoid arthritis, though more research is required.¹⁶

It has been found that a daily dietary supplementation of 4 grams of Omega-3 fatty acids inhibits IL-1 reactivity and suppresses its synthesis.¹⁷ Higher doses (e.g., 9 grams) inhibit the synthesis of TNF.^{16,18,19}

Polyunsaturated Fatty Acids and Chronic Inflammation

Inflammation is regulated by a group of hormones called eicosanoids.¹⁸ They are produced by the Cyclooxygenase 1 and 2 (COX-1 and COX-2) enzyme systems and the Lipoxygenase (LOX) system.

Eicosanoids are synthesized from fatty acids, derived from the diet. Some of these hormones intensify the inflammatory response while others reduce it. How fatty acids get converted to eicosanoids and how current drugs and treatments for inflammation inhibit the system is mapped out in the figure on the following page.

COX-1 and COX-2 enzyme systems and drugs

The COX-1 and COX-2 enzyme systems produce both prostaglandins and prostacyclins.¹⁸ The prostaglandins produced by COX-1 are “good”. They are the "housekeeping" hormones responsible for blood clotting and the health of the kidney, stomach and intestines.²⁰ The COX-2 system produces the “bad” prostaglandins involved in inflammation.

Drugs such as Celebrex and Vioxx block production of the "bad" prostaglandins while not inhibiting the "good" ones. NSAIDs and corticosteroids block production of both the COX-1 and COX-2 enzyme systems which is why they cause intestinal, stomach, internal bleeding, and kidney problems.²¹ Different NSAIDs likely have differing abilities to block the systems, but there is no current research regarding these ratios.²¹ One indication that inflammation is linked to cancer is that use of NSAIDs have been found to prevent certain kinds of colon, lung, mouth, and stomach cancers.⁵

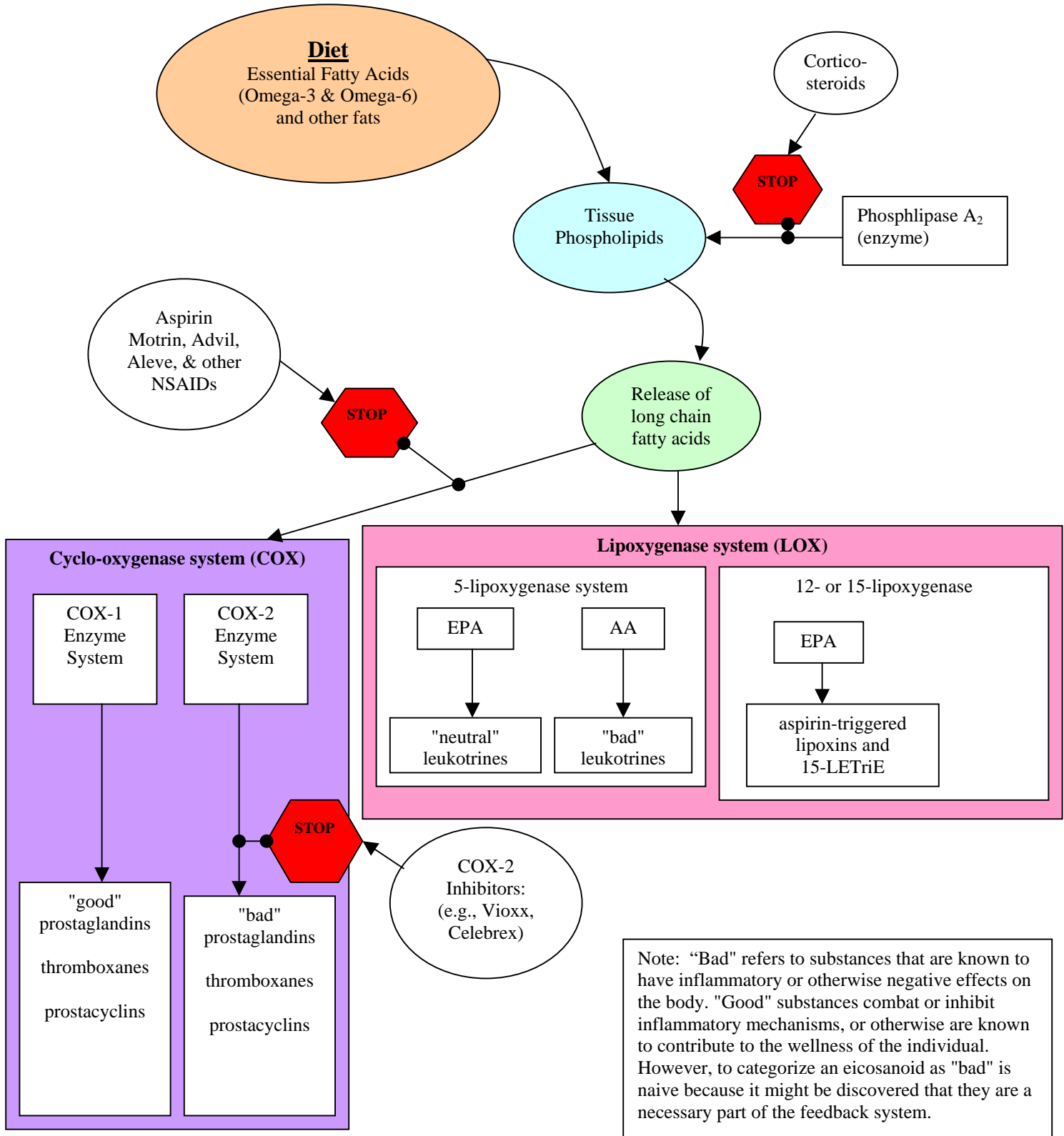
Prostacyclins, produced by the COX-2 system, are responsible for dilating blood vessels and inhibiting blood clots.²⁰ When COX-2 inhibitors are used to treat inflammation, constricted blood vessels and blood clots that aren't broken down in the body can lead to cardiovascular problems.²⁰ This is why Vioxx was pulled from the market and Celebrex is being examined closely for the same reason.

LOX system

The LOX system produces leukotrienes and lipoxins.¹⁸ Leukotrienes, involved in inflammation, are produced by one pathway in the LOX system, 5-LOX.²² These eicosanoids cause vasoconstriction, but increase the permeability of small blood vessels.²³

Another pathway in the LOX system, 15-LOX, produces lipoxins that have the potential to inhibit the action of leukotrienes.²⁴ Interestingly, the presence of aspirin during inflammation can result in the production of aspirin-triggered lipoxins which are powerful anti-inflammatory compounds.^{18,25}

Long-Chain Fatty Acids, Eicosanoid Synthesis, and interference by common treatment methods



Recent research has shown that one of the prostaglandins produced in the COX-2 system (PGE₂), identified as one of the "bad" eicosanoids promoting inflammation, appears to also be a mediator by preventing the generation of pro-inflammatory leukotriens.²⁴ PGE₂ also induces generation of the stop signal lipoxin.²⁴ So, there appears to be a feedback mechanism that occurs in the inflammation process. PGE₂ is perhaps not totally a bad guy after all, since it appears to be involved in inhibiting the inflammatory response of the LOX system.²² 15-LETriE, a lipoxin synthesized by the 15-LOX system, is a powerful inhibitor of the 5-LOX system and the inflammatory leukotrienes it produces.^{18,22}

The role of Omega-3 and Omega-6 fatty acids, trans-fats, and monounsaturated fats

There are two types of polyunsaturated fatty acids (PUFAs) that the body requires and cannot produce itself. The fact that the body cannot create them means that they are essential in the diet, so are termed "essential fatty acids". These two PUFAs, Omega-3 and Omega-6 fatty acids, are converted to eicosanoids unless trans-fats are present. We've all been eating trans-fats for years in processed foods, margarine and shortening. Trans-fats do not occur in nature; they are man-made. Trans-fats inhibit the enzyme needed to transform essential fatty acids into eicosanoids. This may be the reason why they are strongly implicated in the development of heart disease.

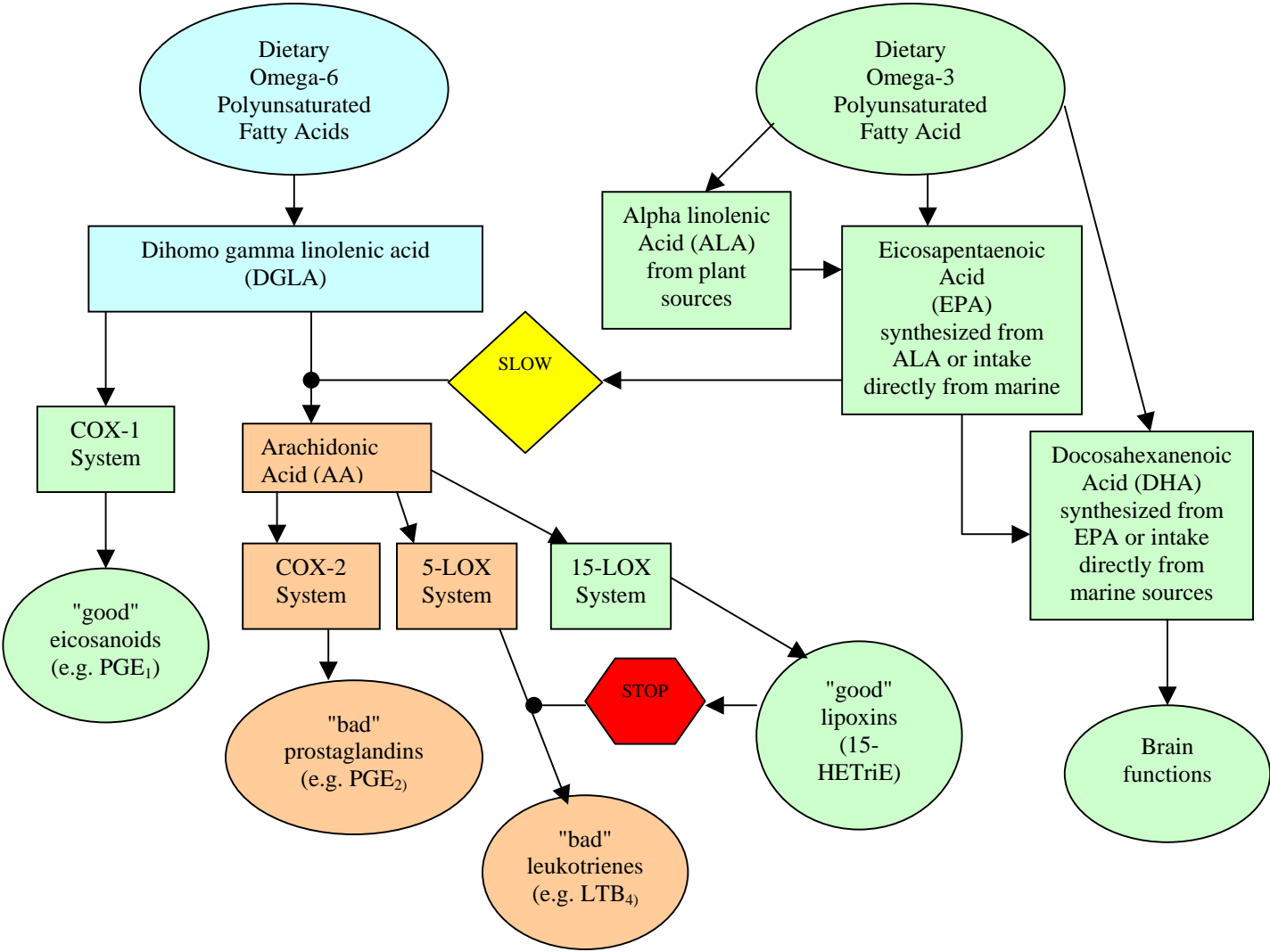
Omega-6 fatty acids can be converted to arachidonic acid (AA) which become "bad" eicosanoids, or they can be converted to "good" eicosanoids.¹⁸ The eicosapentaenoic acid (EPA) of Omega-3 prevents the excess conversion of Omega-6 to AA.¹⁸ Therefore, you cause your body to synthesize more "good" eicosanoids by eating more Omega-3 fatty acids.¹⁸

Omega-3 fatty acids can be obtained from fatty fish or plant oils. The Omega-3 fatty acids from plant sources, such as flax seed, are called alpha-linolenic acid (ALA). They are converted to EPA and docosahexaenoic acid (DHA).^{18,26,27} ALA itself is also an inhibitor of the enzyme needed to form EPA, so it is not easily converted to the long-chain fatty acids EPA and DHA. Only about 10% of ALA is converted to EPA and DHA.²⁷ EPA and DHA are available without this conversion by consuming fish oils, so this is a far better way to ingest Omega-3.^{17,18,24}

All eicosanoids are produced from essential fatty acids in the diet.¹⁸ It is possible to create a balance of fatty acids that promotes more non-inflammatory eicosanoids.^{3,17,26} When fish oil is consumed, EPA is incorporated into cell membranes, partly at the expense of AA.²⁴ Therefore, there is less AA available for synthesis of inflammatory eicosanoids.²⁴ In addition, EPA inhibits the production of inflammatory prostaglandins, thromboxanes, and leukotrienes produced by the COX system.²⁴ In this way, Omega-3 fatty acids can potentially reduce platelet aggregation, blood clotting, smooth muscle contraction, and modulate inflammatory cytokine production and immune function.²⁴ EPA also increases the production of EPA-derived eicosanoids in the COX and 5-LOX systems which are anti-inflammatory in nature.²⁴

Omega-3 fatty acids tend to decrease inflammation and help prevent certain chronic diseases such as heart disease and arthritis.^{3,24,26} The use of Omega-3 fatty acids in therapeutic treatment of chronic inflammatory is promising, especially in the treatment of rheumatoid arthritis.²⁴

THE GRAND SCHEME: OMEGA-3 AND OMEGA-6 PROCESSING



Omega-6 fats, hydrogenated fats and trans-fats increase inflammation by encouraging the synthesis of pro-inflammatory prostaglandins and leukotrienes.^{3,24} Seed oils and plants often contain both Omega-3 and Omega-6 fatty acids.²⁷ Oils from corn, sunflower, soy, peanut and other plants, including flaxseed contain Omega-6 fatty acids (GLA) and the oils of black currant, borage and evening primrose are rich in Omega-6's (GLA).²⁷

Effects of increased Omega-3 fatty acids on immune functioning

Diminishing inflammation and immune cell functions through the use of high doses of Omega-3 fatty acids is generally considered a good thing and beneficial to health. However, reduction of immune cell activity could compromise the ability to defend against infection if taken on a long-term basis.²⁸ A study was conducted to look at the effects of long-term use of either ALA or EPA and DHA on the immune system in doses that would normally be consumed from dietary sources.²⁸ The study found that intake of up to 9.5 gm/day of ALA or up to 1.7 gm/day of EPA+DHA for 6 months does not alter the functional activity of neutrophils, monocytes, or lymphocytes, indicating that the immune system is not changed.²⁸ The fatty acid composition of mononuclear cells was changed, however.

Read more about Omega-3 fatty acids in the next article as we discuss how you can arm your body against inflammation and use natural treatments if you have chronic inflammation.

This article and all of our articles are intended for your information and education. We are not experts in the diagnosis and treatment of specific medical problems. When dealing with a severe problem, please consult with a healthcare professional and research the alternatives available for your particular diagnosis prior to embarking on a treatment plan. You are ultimately responsible for your own health and treatment!

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