

# Backgrounder on Omega-3 Fatty Acids

Flax is rich in the essential omega-3 fatty acid, alpha-linolenic acid (ALA). This chapter provides background information on essential fatty acids and ALA metabolism. Reviewing ALA metabolism in this chapter will make the discussions about ALA's health effects presented in later chapters easier to understand.

## **Essential Fatty Acids**

There are two essential fatty acids (EFAs) in human nutrition: alpha-linolenic acid (ALA), an omega-3 fatty acid, and linoleic acid (LA), an omega-6 fatty acid. Humans must obtain EFAs from foods because the human body cannot make them. EFAs are required for the structure of cell membranes and, because they are unsaturated, they help keep membranes flexible. They are precursors of long-chain fatty acids, some of which are converted to powerful compounds that affect many biological processes, including inflammation and cell signaling (the way cells communicate). EFAs affect gene expression – that is, they turn genes on for the making of cell proteins (45-47). EFAs also have antibacterial actions and are found in breast milk (48). Indeed, breast milk is rich in LA and contains more of ALA than of any other omega-3 fatty acid (49-53).

## Are All Omega-3 and Omega-6 Fatty Acids Essential?

In the strictest sense, there are only two essential fatty acids in human nutrition – alpha-linolenic acid (ALA) and linoleic acid (LA). ALA and LA are required in our diet because our bodies cannot make them. For this reason, ALA and LA are essential nutrients just like calcium, potassium, vitamin C and folate.

The long-chain fatty acids derived from ALA and LA are not essential because the body can make them from ALA and LA. Nonetheless, the long-chain fatty acids in the omega-3 family and many in the omega-6 family are called “essential” in the medical literature because their importance in maintaining health and preventing disease is widely recognized.

## Omega-3 and Omega-6 Fatty Acids

Figure 2 shows the metabolic pathways of the omega-3 and omega-6 fatty acids. Note that ALA is the first or “parent” fatty acid in the omega-3 pathway, reflecting its position as an essential fatty acid. All other omega-3 fatty acids in the pathway can be made from ALA within the body’s cells or obtained from foods. Likewise, LA, being an essential fatty acid, is the parent fatty acid in the omega-6 pathway. All other omega-6 fatty acids can be made from LA within the body’s cells or obtained from foods.

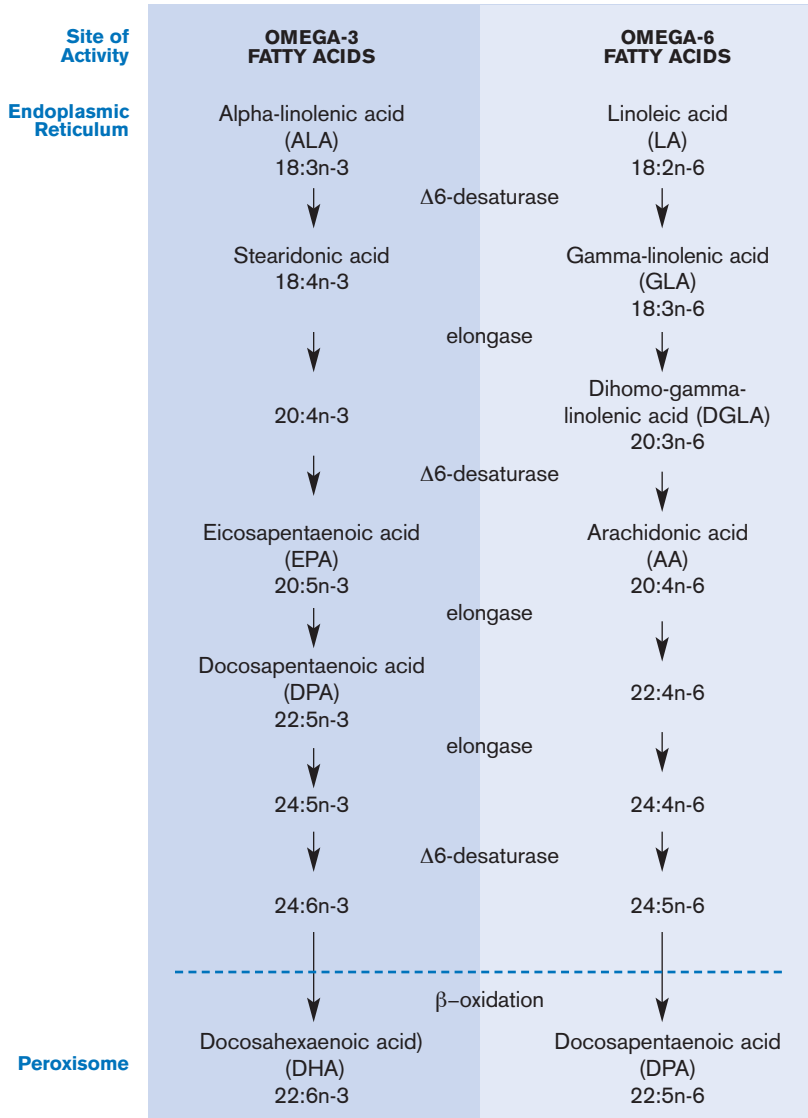
Mammals cannot interconvert the omega-3 and omega-6 fatty acids – they are two separate, distinct families. Furthermore, their metabolism requires the same enzymes, resulting in competition between the two families. An excess of one family of fatty acids can interfere with the metabolism of the other, reducing its incorporation into tissue lipids and altering its biological effects (54,55).

## Metabolism of Alpha-Linolenic Acid (ALA)

About 96% of dietary ALA appears to be absorbed in the gut (56). After absorption, ALA has several metabolic fates: 1) It can undergo  $\beta$ -oxidation to produce energy; 2) It can be recycled to make other fatty acids; 3) It can serve as a substrate for ketogenesis, the process of making ketone bodies; 4) It can be stored in adipose tissue for later use; 5) It can be incorporated into the phospholipids of cell membranes, where it affects membrane activities; and 6) It can be converted to

FIGURE 2

## Metabolic pathways of the omega-3 and omega-6 fatty acids<sup>a</sup>



<sup>a</sup>The conversion pathway shown is the "Sprecher pathway", which is believed to be the major route. Conversion of DPA to DHA via Δ4-desaturase occurs in bacteria and some microorganisms (64). The exact method by which DHA is moved out of the peroxisome is not known, and the factors that affect its translocation have not been identified. New research suggests that regulation of DHA synthesis may be independent of the other steps in the omega-3 pathway (56).

long-chain omega-3 fatty acids like eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA), which have important functions in many types of cells and organs. These metabolic fates of ALA are reviewed in greater detail below.

## 1. $\beta$ -Oxidation

$\beta$ -Oxidation is the process of splitting the carbon chain or backbone of fatty acids into smaller fragments, releasing carbon dioxide (CO<sub>2</sub>) in exhaled breath and producing the energy needed for work, play and rest. The metabolism of ALA contributes significantly to energy production. In men, 24-33% of an ingested dose of ALA undergoes  $\beta$ -oxidation (57-60), whereas the figure is 19-22% in women (61,62). The greater  $\beta$ -oxidation of ALA in men reflects their larger mass of active tissues such as muscles, heart, liver and kidney compared with women. Furthermore, the figures may underestimate by ~30% the actual amount of dietary ALA that undergoes  $\beta$ -oxidation due to the trapping of labeled CO<sub>2</sub> in bicarbonate pools (56).

The amount of ingested ALA shunted into the  $\beta$ -oxidation pathway appears to be stable and is not affected by dietary intake. In a study of 14 healthy men aged 40-64 years, the proportion of ALA undergoing  $\beta$ -oxidation did not differ between the men who consumed a diet rich in ALA (10 g/day) versus those who consumed a diet rich in EPA + DHA (1.5 g/day) for 8 weeks (58).

## 2. Recycling of ALA carbon

Some of the carbon fragments produced during  $\beta$ -oxidation of ALA are not oxidized for energy but are recycled into saturated and monounsaturated fatty acids. The recycling of ALA carbon appears to be an important source of fatty acids during pregnancy (56).

## 3. Ketone body formation

Canadian and U.S. researchers recently proposed a new function for ALA – ALA plays an important role in maintaining brain function during aging, not by its conversion to longer-chain omega-3 fatty acids, but by being used to make ketone bodies (63). ALA is preferred over LA or oleic acid as the substrate for ketogenesis – the process of making ketone bodies. Even though the brain's main energy source is glucose, it uses ketone bodies as an alternative energy source during fasting or illness. As we age, the brain's ability to take up glucose is reduced, especially in patients with Alzheimer disease. High-fat diets enriched

with ALA may produce a mild ketonemia that could help retain or restore cognitive function in the elderly. The researchers suggest that ALA and its long-chain metabolites each have a unique, beneficial role to play in maintaining brain function during aging.

#### 4. Storage in adipose tissue

Adipose tissue makes up about 15% of body mass in men and 23% of body mass in women. ALA storage in adipose tissue is a reserve supply which can be called on when the demand for ALA increases. In a typical 75 kg man with a fat mass of 15%, adipose tissue is calculated to contain 79 g of ALA. In a typical 65 kg woman with a fat mass of 23%, adipose tissue is calculated to contain 105 g of ALA (54). The greater capacity for ALA storage by women reflects their greater fat mass compared with men.

#### 5. Incorporation into phospholipids

Phospholipids are structural elements in cells. All human cell membranes contain a double layer of phospholipids. Phospholipids consist of fatty acids, and the types of fatty acids they contain affect membrane flexibility, the transfer of nutrients across the membrane and how cells communicate with one another. Diets high in saturated fatty acids result in a high level of saturated fatty acids in membrane phospholipids, which makes the membrane more rigid and less responsive to signals from other cells. Diets high in polyunsaturated fatty acids increase the level of polyunsaturated fatty acids in membrane phospholipids, making them more flexible and responsive (48). Dietary ALA is incorporated into membrane phospholipids (54).

#### 6. Conversion to longer-chain omega-3 fatty acids

ALA is converted to longer-chain omega-3 fatty acids by a series of alternating desaturations and elongations, as shown in **Figure 2**. The desaturations add a double bond by removing hydrogen, while the elongations add two carbon atoms (64). The main long-chain omega-3 fatty acids formed from the desaturation and elongation of ALA are EPA, DPA and DHA.

**EPA.** Estimates of the amount of ALA converted to EPA range from 0.2% to 8% (54,57), with young women showing a conversion rate as high as 21% (61).

**DPA.** Conversion of ALA to DPA is estimated to range from 0.13% to 6% (56). The conversion rate for young women is on the higher end (6%) (61).

**DHA.** Conversion of ALA to DHA appears to be limited in humans, with most studies showing a conversion rate of about 0.05% (56,65), although one study reported a figure of 4% (66). A conversion rate of 9% was reported in young women (61).

The large differences in the rates of ALA conversion reflect major differences in the studies' methods. There is a need for more research to resolve the issue of how much ALA is converted to longer-chain omega-3 fatty acids in humans of all ages.

## Factors affecting ALA conversion to EPA, DPA and DHA

ALA conversion to its longer-chain metabolites is affected by diet. Other factors affecting its conversion have also been identified.

**GENDER.** Women of child-bearing age have the capacity to convert more ALA to EPA and DHA than men do (61), possibly due to their greater estrogen levels – estrogen is a sex hormone that appears to regulate DHA synthesis – in addition to their greater need for DHA during pregnancy and their lower rates of  $\beta$ -oxidation of ALA (54,61). Young women may also be more sensitive to diet than men. In one study, young women converted more ALA to DHA when they ate a beef-based diet than young men did (67,68).

**DIET.** A diet rich in LA reduces ALA conversion by as much as 40% (66). In a study of 22 healthy men, an LA-rich diet (10.5% energy) reduced the EPA content of plasma phospholipids significantly after four weeks compared with a low-LA diet (3.8% energy), even though both diets contained the same amount of ALA (1.1% energy) (69). In addition, pregnant women with a high LA intake had lower EPA and DHA levels in umbilical plasma, suggesting reduced ALA conversion and availability of omega-3 fatty acids for the developing fetus (70). The absolute amounts of ALA and LA in the diet appear to be more important in determining ALA conversion than their dietary ratio (71).

Other dietary factors that interfere with ALA conversion include the intake of dietary cholesterol (72,73), saturated fat, oleic acid (74,75), *trans* fatty acids (76,77) and alcohol (48) and the ratio of polyunsaturated to saturated fats in the diet (78). High intakes of EPA and DHA can also block ALA conversion, possibly by signaling that tissue levels of omega-3 fats are adequate. Furthermore, a diet containing more than 12 g of ALA per day can reduce ALA conversion (79).

**CIGARETTE SMOKING.** Smoking affects the metabolism of omega-3 fatty acids. In an *in vitro* (test tube) study, human cells taken from breast tissue were exposed to cigarette smoke bubbled into the growth medium. Breast cells exposed to cigarette smoke converted less ALA to EPA and DHA. The enzyme most affected by the cigarette smoke was  $\Delta 5$ -desaturase (see **Figure 2**). Exposure to even low doses of cigarette smoke had a negative effect on the metabolism of omega-3 fatty acids in human breast cells (80).

## Metabolism of Omega-6 Fatty Acids

Like the metabolism of ALA, LA is converted to long-chain omega-6 fatty acids by a series of desaturations and elongations. (Refer to **Figure 2**.) Three fatty acids in the omega-6 pathway are worth noting. Gamma-linolenic acid (GLA) is separate and distinct from ALA, the essential omega-3 fatty acid, and the two fatty acids should not be confused. GLA is converted to dihomo-gamma-linolenic acid (DGLA), a precursor of certain eicosanoids that tend to be somewhat mild in their biologic effects. GLA is found in evening primrose, borage and black currant oils.

Arachidonic acid (AA) is the precursor of powerful eicosanoids, several of which promote the clumping (aggregation) of blood platelets, the clotting of blood within blood vessels (thrombosis) and inflammatory reactions. AA is the most tightly regulated fatty acid in cell membrane phospholipids because it affects the way cells behave, and its actions have far-ranging effects (81). Diets high in LA or AA may result in an over-abundance of AA-derived eicosanoids that, in turn, may result in an over-active immune system that contributes to chronic diseases like coronary heart disease, diabetes and cancer (82-85).

Docosapentaenoic acid (DPA) with the formula  $22:5n-6$  is a member of the omega-6 family. It should not be confused with the omega-3 DPA ( $22:5n-3$ ).

## Biologic Effects of Omega-3 Fatty Acids

The omega-3 fatty acids have biologic effects that make them useful in preventing and managing chronic conditions such as type 2 diabetes, kidney disease, rheumatoid arthritis, high blood pressure, coronary heart disease, stroke, Alzheimer disease, alcoholism and certain types of cancer (48). Key biologic effects of the three main omega-3 fatty acids – ALA, EPA and DHA – are described below.

### Alpha-linolenic acid (ALA)

ALA has several biologic effects, which together contribute to its positive health effects:

1. Breast milk contains about 0.5-2.0% ALA and about 0.1-0.4% DHA (86) or roughly five times more ALA than DHA. ALA constitutes 75-80% of the total omega-3 fatty acids in breast milk (49,51-53), supporting a role for ALA in the growth and development of infants.
2. ALA is required for maintaining the nervous system. In humans, a deficiency of ALA results in poor growth and neurological problems such as numbness, weakness, pain in the legs, inability to walk and blurring of vision (87). These clinical deficiency symptoms can be alleviated by adding ALA to the diet (24,87-91).
3. ALA is the precursor of EPA, DPA and DHA. Thus, ALA-rich diets increase the ALA, EPA, DPA and total omega-3 fatty acid content of cell membrane phospholipids. In one study of 20 healthy men and women taking six flax oil capsules a day (providing 3.5 g of ALA/day) for 8 weeks, the ALA content of red blood cell membranes increased 100%, the EPA content increased 33%, and the DPA content increased 20%; the DHA content was unchanged (92). In other studies, diets containing more than 4.5 g of ALA/day (contained in about 1/2 tbsp of flax oil or 2 heaping tbsp of milled flax daily) increased the EPA content of plasma phospholipids between 33% and 370% and the DPA content between 5% and 50% (54). [The large ranges in the response of study volunteers to dietary ALA reflect differences in the amount of LA in their diets, among other factors (55).] Increasing the omega-3 fatty acid content of cell membrane phospholipids increases their flexibility and alters the way they behave in beneficial ways (93).

4. ALA dampens inflammatory reactions by blocking the formation of compounds that promote inflammation. Inflammation is a feature of many chronic diseases, such as heart disease, type 2 diabetes, metabolic syndrome, obesity, cancer and Alzheimer disease (94-96). ALA has several anti-inflammatory actions:

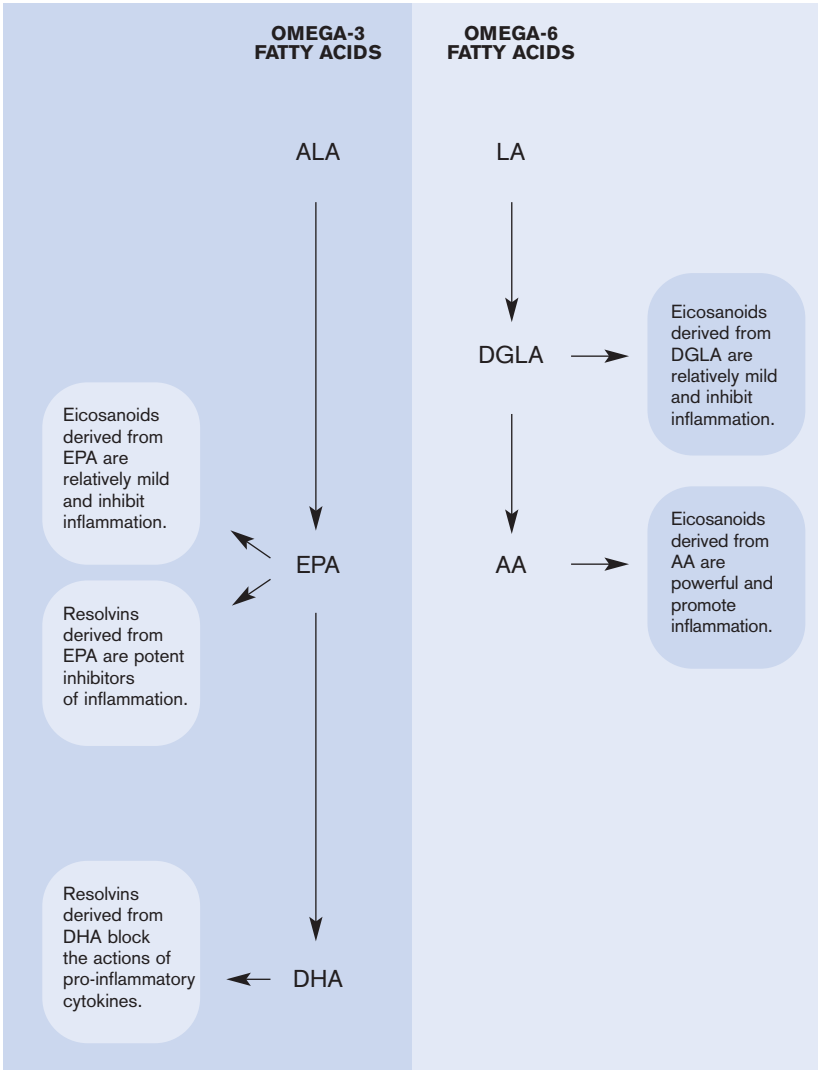
- **EICOSANOIDS.** ALA affects eicosanoids in two ways. First, ALA is a precursor of EPA, which is itself a precursor of eicosanoids, as shown in **Figure 3**. Eicosanoids control inflammatory reactions. Their release is a normal response to injury, and their actions are required to help repair damaged tissue. However, not all eicosanoids are alike. The eicosanoids derived from EPA tend not to promote inflammation. This is one reason why nutrition experts advise consumers to eat more omega-3 fatty acids: A diet rich in omega-3 fatty acids produces more beneficial eicosanoids and less inflammation and decreases the risk of chronic diseases compared with diets rich in omega-6 fatty acids.

Secondly, ALA interferes with the conversion of LA to AA and blocks the conversion of AA to its pro-inflammatory eicosanoids. For example, diets rich in ALA decreased significantly the concentration of AA in neutrophils (97) and in serum (98,99). The production of eicosanoids from AA in mononuclear cells decreased 30% in healthy men who consumed flax oil for four weeks (100). [Neutrophils and mononuclear cells are types of immune cells that help control infections and inflammation.]

- **CYTOKINES.** ALA blocks the formation of cytokines. Three cytokines that contribute to inflammation are tumor necrosis factor  $\alpha$ , interleukin-1 $\beta$  and interleukin-6. A study of 20 men and women with high blood cholesterol found that the production of these cytokines by certain immune cells was decreased significantly when the volunteers ate a diet high in ALA compared with an average American diet. The high-ALA diet in this study provided about 19 g ALA/day obtained from walnuts, walnut oil and flax oil (99).

FIGURE 3

## Sources and actions of eicosanoids and resolvins



ALA (alpha-linolenic acid) is converted to EPA (eicosapentaenoic acid), which in turn can be converted to certain eicosanoids that are relatively mild in their biologic effects and tend not to promote inflammation. The eicosanoids derived from dihomo-gamma-linolenic acid (DGLA) are like those derived from EPA. Many of the eicosanoids derived from arachidonic acid (AA) are powerful and control immune reactions and inflammation. EPA and docosahexaenoic acid (DHA) can be converted to anti-inflammatory compounds called resolvins.

- **PLATELETACTIVATING FACTOR.** ALA may help block the formation of platelet-activating factor (PAF). In studies of mice used as a model of lupus nephritis (kidney inflammation), feeding flax in the diet for 14 weeks blocked PAF-caused platelet aggregation. According to the researchers, ALA may work synergistically with flax lignans to dampen the effects of PAF (101).
- **C-REACTIVE PROTEIN.** High blood levels of C-reactive protein (CRP) indicate the presence of systemic inflammation or infection (102). In a clinical trial, serum CRP levels decreased 75% when men and women ate a high-ALA diet containing walnuts, walnut oil and flax oil for 6 weeks (98).

## Regulators and Indicators of Inflammation

**C-reactive protein (CRP)** – is produced early in the body's response to inflammation or infection and is also an indicator of systemic (overall body) inflammation.

**Cytokines** – are proteins liberated from immune cells in response to injury, infection or exposure to foreign substances; they cause fatigue and sleepiness in people recovering from bacterial and viral infections.

**Eicosanoids** – control many body functions, especially those related to inflammation, and serve as cell messengers in nervous tissue like the brain; some eicosanoids promote inflammation, while others tend to block it.

**Platelet-activating factor (PAF)** – controls inflammation and shock, causes platelet aggregation, activates immune system cells and promotes the release of arachidonic acid; at high concentrations it can cause life-threatening asthma-like symptoms.

**Resolvins** – are formed from EPA and DHA; these compounds help limit inflammatory reactions by putting the brakes on inflammation.

## **Eicosapentaenoic acid (EPA)**

EPA is the precursor of certain eicosanoids that tend not to promote inflammation because they are less biologically active than those derived from arachidonic acid (83). EPA affects inflammation in another way: It gives rise to potent compounds called resolvins, so named because they are found at sites recovering from inflammation (that is, when the inflammation is resolving) (103). The EPA-derived resolvins dampen inflammatory reactions (104).

## **Docosahexaenoic acid (DHA)**

In the fetus and infant, DHA is required for the development and maturing of the eye, where it constitutes as much as 80% of total polyunsaturated fatty acids in the retina, and of the brain and nervous system, which contain high concentrations of DHA (105). The brain, retina and sperm have the highest concentrations of DHA of any tissue in the body (106). The demand for DHA is highest during the latter part of pregnancy and in the first few months of infancy. Like EPA, DHA also gives rise to resolvins. The DHA-derived resolvins are active in the brain, where they block the actions of pro-inflammatory cytokines (104).