# Essentiality of Fatty Acids

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**ABSTRACT:** All fatty acids have important functions, but the term "essential" is applied only to those polyunsaturated fatty acids (PUFA) that are necessary for good health and cannot be completely synthesized in the body. The need for arachidonic acid, which is utilized for eicosanoid synthesis and is a constituent of membrane phospholipids involved in signal transduction, is the main reason why the n-6 class of PUFA are essential. Physiological data indicate that n-3 PUFA also are essential. Although eicosapentaenoic acid also is a substrate for eicosanoid synthesis, docosahexaenoic acid (DHA) is more likely to be the essential n-3 constituent because it is necessary for optimal visual acuity and neural development. DHA is present in large amounts in the ethanolamine and serine phospholipids, suggesting that its function involves membrane structure. Because the metabolism of n-6 PUFA is geared primarily to produce arachidonic acid, only small amounts of 22-carbon n-6 PUFA are ordinarily formed. Thus, the essentiality of n-3 PUFA may be due to their ability to supply enough 22-carbon PUFA for optimal membrane function rather than to a unique biochemical property of DHA.

Fatty acids carry out many functions that are necessary for normal physiological function and good health. Saturated fatty acids are involved in energy production, energy storage, lipid transport, the synthesis of phospholipids and sphingolipids needed for membrane synthesis, and the covalent modification of many regulatory proteins. Monounsaturated fatty acids also are involved in many of these processes and play a key role in maintaining optimal fluidity of the membrane lipid bilayer. Although these are clearly vital physiological processes, the term "essential" is not applied to the saturated or monounsaturated fatty acids. The designation is reserved for those polyunsaturated fatty acids (PUFA) that are required for good health and, in addition, cannot be completely synthesized in the body. As it is presently used, essentiality implies that the fatty acid not only performs a vital function, but it also is a required dietary nutrient.

*Essential fatty acids.* PUFA have important effects on the structure and physical properties of localized membrane domains and, in addition, are involved in eicosanoid production, signal transduction, and the activation of nuclear transcription factors. Two classes of PUFA, designated as n-6 and n-3, normally are present in the tissues and body fluids. Neither of these classes can be completely synthesized by mammalian cells and, therefore, they must be obtained from the diet. The usual Western diet contains 10- to 20-times more n-6 than n-3 PUFA, and the plasma and most other tissues also contain 10- to 20-times more n-6 fatty acid. The exceptions are the brain and retina which are rich in n-3 PUFA.

A very serious systemic illness called essential fatty acid deficiency occurs if the body becomes deficient in n-6 PUFA. A similar debilitating disease does not occur if there is a deficiency in n-3 PUFA. However, accumulating evidence indicates that n-3 PUFA are required for optimal health, especially for normal neural development and visual function (1,2), and there is an increasing consensus that they, too, are essential fatty acids.

*Mechanism of action of the essential fatty acids.* Table 1 lists the biochemical actions of the key members of the n-6 and n-3 classes of essential fatty acids. The need for arachidonic acid (20:4n-6) almost certainly is the primary reason why n-6 PUFA are essential. Arachidonic acid is the main substrate for synthesis of the eicosanoid mediators produced by the cyclooxygenase, lipoxygenase, and cytochrome P450 pathways (3), and it is highly enriched in the inositol phospholipids that are involved in signal transduction (4). Linoleic acid (18:2n-6) also probably is essential because it is utilized for the synthesis of the complex lipids that form the permeability barrier of the epidermis (5).

The biochemical reason that the n-3 PUFA are essential is not presently known. In fact, it is not certain whether eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), or both carry out the essential biochemical functions. Like arachidonic acid, EPA (20:5n-3) is a substrate for eicosanoid synthesis (6), and EPA competes with arachidonic acid for the same metabolic pathways (7,8). However, no requirement for the eicosanoids produced from EPA has so far been demonstrated, and very little EPA is present in the tissues of individuals who consume the usual Western diet. Therefore, competition with arachidonic acid seems improbable unless an individual is consuming supplemental amounts of EPA. Under ordinary conditions, DHA (22:6n-3) is the most abundant n-3 PUFA contained in the tissues, especially in the brain and retina. For this reason, it seems more likely that DHA rather than EPA is the essential n-3 component.

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Abbreviations: DHA, docosahexaenoic acid; n-6 DPA, n-6 docosapentaenoic acid; EPA, eicosapentaenoic acid; PUFA, polyunsaturated fatty acid(s).

**TABLE 1**
**Biochemical Functions of the n-6 and n-3 Fatty Acids**

| Class | Fatty acid | Function |
|---|---|---|
| n-6 | Arachidonic | Eicosanoid synthesis<br>Component of the inositol phospholipids |
| n-6 | Linoleic | Synthesis of lipids that form the epidermal permeability barrier |
| n-3 | Eicosapentaenoic | Eicosanoid synthesis<br>Structural analog and competitor of arachidonic acid |
| n-3 | Docosahexaenoic | Structure of membrane lipid domains<br>Modulation of integral membrane proteins<br>Metabolism of phosphatidylethanolamine, ethanolamine plasmalogens, and phosphatidylserine<br>Formation of free radicals<br>Regulation of gene expression |

*DHA function.* Considerable effort is being expended to determine the biochemical functions of DHA, and some recent progress has been made. DHA is contained primarily in three phospholipids, phosphatidylethanolamine, ethanolamine plasmalogens, and phosphatidylserine (9,10). This suggests that it may affect the trafficking or metabolism of these phospholipids, or it may produce structural changes in regions of the membrane lipid bilayer that are enriched in these phospholipids (11). Numerous effects produced by DHA are consistent with a membrane lipid effect. For example, DHA modulates the carrier-mediated transport of choline, glycine and taurine (12–14), the function of delayed rectifier potassium channels (15), and the response of rhodopsin contained in phospholipid vesicles (16). Specific interactions of phospholipid fatty acyl chains with membrane proteins could account for each of these effects. Other actions of DHA include the formation of free radicals in response to oxidative stress (17), transcriptional activation of genes (18), and the prevention of apoptosis (19). One or more of these effects probably constitutes an essential biochemical or developmental function and, hence, the molecular reason why DHA is essential.

*Elongation and desaturation of n-3 and n-6 fatty acids.* The same elongation and desaturation pathway involving 24-carbon intermediates and peroxisomal retroconversion is utilized by n-3 and n-6 PUFA (20). Studies of this process in cultured brain cells indicate that this pathway operates primarily in astrocytes and that the astrocyte pathway handles n-3 and n-6 PUFA differently (21). These differences are illustrated in Figure 1. DHA is the main product formed when the astrocytes are incubated with [1-$^{14}$C]linolenic acid, whereas arachidonic acid is the main product when they are incubated with an equivalent amount of [1-$^{14}$C]linoleic acid (21). DHA and arachidonic acid also are the main products released into the extracellular fluid during these incubations. About 20-times more DHA than n-6 docosapentaenoic acid (n-6 DPA), the corresponding 22-carbon fatty acid of the n-6 series, is formed by the astrocytes under these conditions. Furthermore, 10-times more radiolabeled DHA than n-6 DPA accumulates in the astrocytes, and 45-times more DHA is released into the medium.

Additional studies indicate that neurons cultured under similar conditions do not produce either DHA or DPA from n-3 or n-6 PUFA precursors, respectively (21). Therefore, the neurons apparently are dependent on an external source for these fatty acids, and it seems likely that they are supplied at least in part by release from the astrocytes (22). As described above (21), the astrocytes produce and release much more DHA than w-6 DPA. Taken together, these metabolic results probably explain why the brain accumulates DHA rather than n-6 DPA even though n-6 PUFA are usually much more abundant.

*Basis for n-3 fatty acid essentiality.* It is generally assumed that the n-3 class of PUFA is essential because the function of one of its components, probably DHA, is necessary and cannot be fully replaced by any other fatty acid. Because n-6 DPA has the same structure as DHA except for the Δ19 double bond, the unique action of DHA must somehow involve the methyl-end of its hydrocarbon chain.

While this remains the most likely biochemical explanation for the essentiality of the n-3 fatty acids, an alternative possibility should be considered in view of the astrocyte results

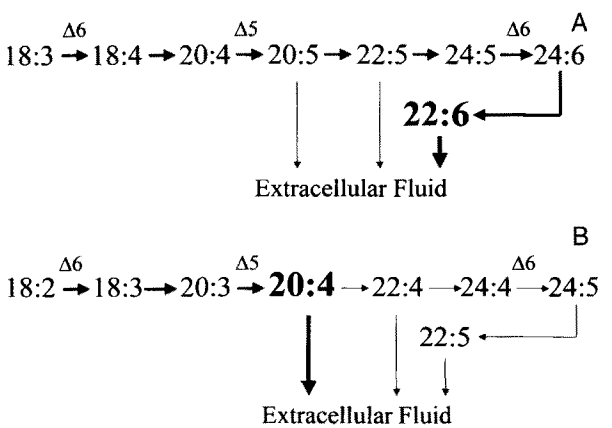


**FIG. 1.** Operation of the polyunsaturated fatty acid metabolic pathway in murine brain astrocyte cultures. A) illustrates the function of this pathway with n-3 fatty acids, B) with n-6 fatty acids. The fatty acids and arrows shown in bold type signify the main products that are formed and released to the extracellular fluid. Thus, docosahexaenoic acid (22:6) is the most abundant n-3 fatty acid product formed and released, whereas arachidonic acid (20:4) is the main n-6 product.

(21,22). It is possible that the fundamental need of the central nervous system is for a 22-carbon, highly unsaturated fatty acid containing a Δ4 double bond. Even though n-6 PUFA precursors are more abundant, enough n-6 DPA cannot be formed in the brain to fulfill this requirement because the astrocyte metabolic pathway utilizes n-6 PUFA primarily to produce arachidonic acid. By contrast, the pathway synthesizes mainly 22-carbon fatty acids from n-3 precursors, and DHA is the main product. Thus, n-3 PUFA may be essential because they are the only class that can generate a sufficient amount of a 22-carbon, unsaturated fatty acid containing a Δ4 double bond to satisfy the needs of the central nervous system.

The argument against this metabolic hypothesis is that although n-6 DPA replaces DHA when there is an n-3 PUFA deficiency, it does not completely overcome the functional deficit. However, recent findings in the rat pineal gland indicate that even though n-6 DPA increases during n-3 PUFA deficiency, it does not fully replace DHA (23). Although the decrease in total n-3 PUFA was almost entirely replaced by n-6 PUFA, arachidonic acid and docosatetraenoic acid (22:4n-6) accounted for about 50% of the replacement. There was a 12-fold increase in n-6 DPA, but the total pineal lipids contained only about half as much n-6 DPA as compared with the amount of DHA normally present. The reduction in n-6 DPA relative to the normal amount of DHA was especially evident in molecular species of phosphatidylethanolamine and ethanolamine plasmalogen that contain stearic acid.

Based on these observations, it appears that the functional abnormalities in n-3 PUFA deficiency may be due to an inability to fully replace the loss of DHA with n-6 DPA. If so, the quantitative differences in the products formed by the elongation and desaturation pathway with n-3 and n-6 fatty acids may be the underlying biochemical reason why n-3 PUFA are essential.

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