NUTRI NEWS

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THE IMPACT OF ESSENTIAL FATTY ACIDS ON THE AGING PROCESS

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For normal function, the human body generates most of the fat it requires from carbohydrates (e.g.., starches and sugars). However, the human system is incapable of producing certain "essential" fats. These fats, collectively, are known as essential fatty acids (EFAs). They are found in virtually all types of foods, but are most prevalent in certain types of oils.

EFAs fall into two specific groups, distinguished by their chemical configurations. Although they are part of the same family, these two groups do not function in the same capacity. In fact, they have been shown to compete against one another within the body's metabolic pathways.

In 1929, Burr and Burr discovered that certain fatty acids are essential components of the diet. They also determined that mammals were unable to synthesize linoleic (LA - 18:2n-6) or α-linolenic (ALA - 18:3n-3) acids.

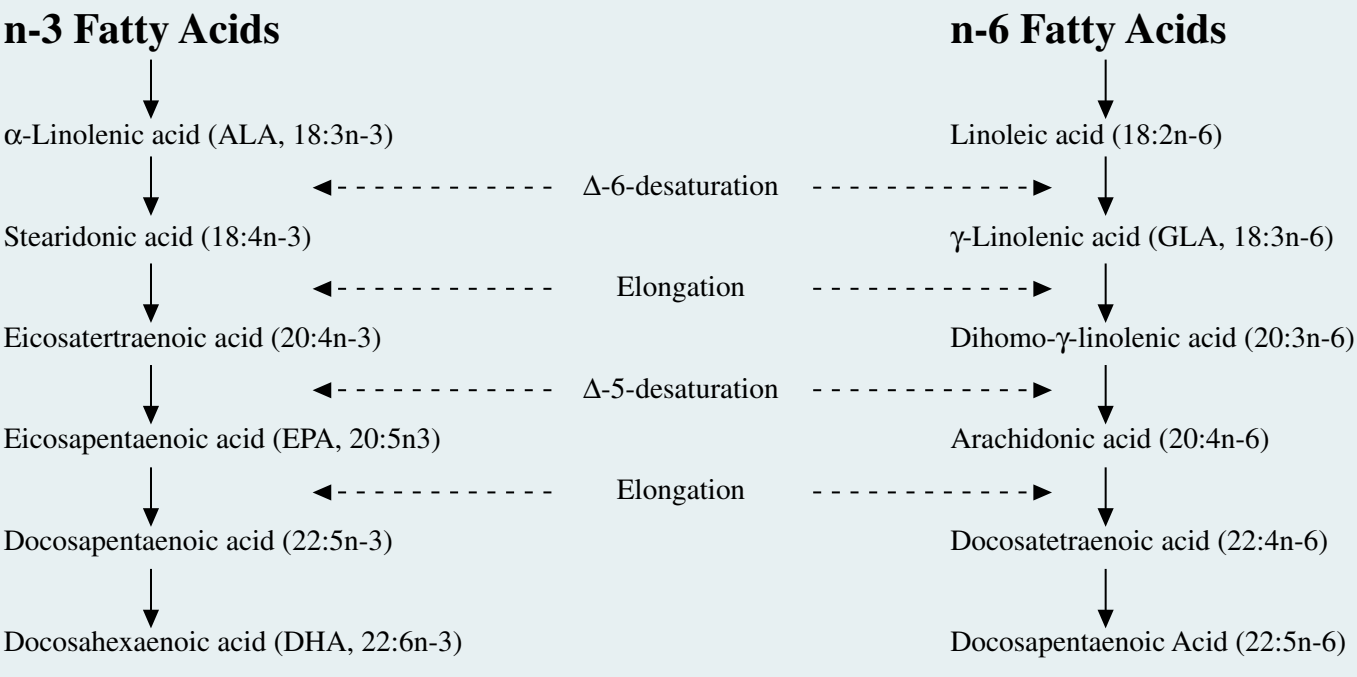
Defining essential fatty acids

The notations "n-6" and "n-3" represent the position of the first double bond when counting from the methyl end of the fatty acid. Those fatty acids, with their first double bond 3 carbons from the methyl end, are commonly referred to as omega-3 fatty acids. Those with their first double bond 6 carbons from the methyl end are termed omega-6 fatty acids.

Humans, as well as other species within the animal kingdom, lack the capacity for de novo synthesis of fatty acids that contain a double bond within the last 6 carbons from the methyl end. Consequently, they must rely on dietary sources for these fatty acids.

The metabolites that LA and ALA generate are the most important factor in the structure and function of every cell within the body.

Essential Fatty Acid Metabolism



Interestingly, LA and ALA themselves carry out few of the functions of essential fatty acids. For example, LA helps maintain the water impermeability of the skin, but without further metabolism, it is unable to carryout other functions. LA and ALA must be metabolized to other fatty acids before potent biological functions become apparent. Figure 1 shows the pathways by which LA and ALA from the diet are metabolized.

The first step in the metabolism of both LA and ALA is a desaturation by the enzyme D-6-desaturase. This enzyme inserts a double bond and converts LA and ALA into gamma-linolenic acid (GLA, 18:3n-6) and stearidonic acid (18:4n-3), respectively. After further desaturation and elongation, LA is ultimately converted to arachidonic acid (AA, 20:4n-6) and docosapentaenoic acid (DPA, 22:5n-6). ALA is converted to eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3).

Because of our knowledge of these metabolic pathways, EPA, DHA, and GLA are now commonly categorized as EFAs, as they depend on the presence of LA and ALA for their synthesis. However, unlike other animals, such as the rat, we have a limited ability to convert ALA to EPA and DHA. Consequently, we depend greatly on dietary sources of EPA and DHA.

Omega-3 fatty acids

EPA and DHA are commonly referred to as "omega-three EFAs" or "omega-3 fatty acids (FAs)," since the first double bond is 3 carbons from the methyl end, as previously mentioned. These omega-3 FAs comprise the smaller family of EFAs, and are typically found in higher concentrations in fish oils and linseed (flaxseed) oil. Omega-3s are also found in many of the green leafy vegetables, where they are associated with the chloroplasts, and in the meat of animals that feed on grass (herbivores). Interestingly, it is only within the chloroplasts of plants that enzymatic reactions can desaturate linoleic acid (n-6) to yield alpha-linolenic acid (n-3).

Our ancestors consumed high concentrations of omega-3 FAs, as their diets included only what they could hunt (meat) or gather (green leafy vegetables).

The human brain is high in omega-3 FAs. Scientists have attributed the neurological evolution and development of modern humans to the high omega-3 FA diets that our ancestors consumed. However, as humans have evolved, a systematic erosion of omega-3 FAs has occurred our diet. This is most evident in the last 100 years, and especially in Western society. Some medical authors claim that the largest known nutritional deficiency in modern-day society is that of omega-3 FAs. Some scientists and clinicians have postulated and proven that many of the chronic, insidious disease processes that are typically attributed to aging, actually reflect a chronic state of omega-3 deficiencies. These deficiencies sometimes occur throughout most of the patients' life spans.

Omega-3 (as well as omega-6) FAs serve as precursors for a vast number of signal molecules (hormone-like substances that act as messenger molecules). These signal molecules include prostaglandins, leukotrienes, thromboxanes, and other eicosanoids that are involved in numerous biological functions. The omega-3 FAs are incorporated within all the phospholipid bilayers of cell membranes, and interact with nuclear receptor proteins. However, they do not have the same susceptibilities as other acid substrates.

Omega-6 fatty acids

The omega-6 FAs comprise the larger of the two EFA families. Omega-6 FAs are predominantly found in most seed and vegetable oils, including primrose oil, borage seed oil, corn oil, safflower oil, and sunflower oils. Like omega-3 FA deficiencies, chronic omega-6 FA deficiencies have also been proven to impair the human system. (This will be discussed later in this chapter.) Some studies indicate a correlation between excess consumption of omega-6 FAs and the risk for developing certain diseases. This is very plausible, considering our modern society's increased dependency on vegetable oils, especially over the last 100 years.

Benefits of EFAs

Classic signs of EFA deficiency are dermatitis, growth retardation, and reproductive failure. However, EFAs are now known to exert many other wide-ranging, health-promoting effects. This chapter will focus on the importance of EFAs in various physiologic functions.

How EFAs work

Science is learning more about the biochemistry and physiology of EFAs. We are beginning to understand how they function beyond their ability to prevent classic signs of deficiency.

A number of mechanisms have been explored in an attempt to explain the essentiality of these compounds, including their effect on membrane structure. This is a seemingly simple role, but it should not be overlooked. A change in the fatty acid composition of the diet can easily modify membrane fluidity and structure. Even the insertion of one additional double bond into a membrane can significantly change the properties and physiologic functions of a membrane. These shifts can take the form of altered protein-protein interactions, altered protein-lipid interactions, changes in cellular receptors and their substrate-binding abilities, loss or gain in the ability to transport certain molecules across the membrane, and other functions that can have a profound impact of how a cell or tissue functions.

EFAs and insulin resistance

Research has shown the significance of the polyunsaturated omega-3 FAs in the maintenance of cellular membrane fluidity, and the resulting insulin receptor responsiveness. The high prevalence of diabetes and insulin resistance in the Pima Indians of Arizona is an excellent example of how EFAs affect cell membranes, and ultimately the clinical progression of type 2 diabetes (non-insulin-dependent diabetes mellitus [NIDDM]).

Type 2 diabetes has been termed "adult-onset diabetes," although it is now being diagnosed in children throughout the United States. It usually develops due to dietary and sedentary factors. Type 2 diabetes is not due to a lack of insulin. Rather, it is a consequence of insulin insensitivity, or perhaps more appropriately, insulin resistance. If insulin levels are measured in these patients, they are found to be significantly higher than normally expected. Yet, the glucose levels in these patients are normal to borderline, and actually represent a compensated glucose level.

What actually occurs is that the body registers higher glucose levels, and interprets this incorrectly as not having sufficient insulin. The body attempts to compensate for the higher levels of circulating glucose by increasing insulin output. It tries to use the additional insulin to drive glucose into the cells, in order to reduce glucose levels in the bloodstream.

Temporarily, this higher insulin output works; it effectively pushes the excess glucose into the cells and decreases serum glucose levels. However, although glucose levels may be normal, insulin levels are high due to the compensatory aspect. Eventually, the body's ability to produce insulin is maximized, and the pancreas can no longer compensate by increasing insulin output. It is at this point that the clinician usually begins to observe serum glucose levels increasing.

The primary problem, however, is not the increasing levels of glucose. Rather, it is the resultant increased need for insulin due to insulin resistance. Therefore, it is actually possible to screen for diabetes by simply measuring insulin levels. If insulin levels are high, then the body is "resisting" the effects of insulin. The disease process is usually progressive unless insulin resistance is recognized and appropriate treatment initiated.

Problem diets

The diets of insulin-resistant patients are typically high in simple carbohydrates. Due to their sedentary lifestyle, the carbohydrates these patients ingest are not utilized and eventually get stored as fat. This explains why patients with type 2 diabetes are usually found to be obese.

Furthermore, insulin-resistant patients frequently eat an excess of fried foods (e.g., french fries, hamburgers) and fat. Fried foods are usually prepared in oils from the omega-6 FA family, or from animal fats. Higher consumption of omega-6 FAs leads to a higher n-6 (omega-6) to n-3 (omega-3) fatty acid ratio. The ratio should ideally be 1:1, or at least 4:1. However, the current ratios of omega-6 to omega-3 FAs seen in modern-day society can be as high as 40:1.

Impact of omega-3 FAs on cell membranes

Omega-3 FAs of a specific type are known to increase the cell membrane sensitivity to the effects of insulin. In contrast, omega-6 FAs have been found to increase the resistance of the cell membrane to the effects of insulin.

One study focused on the modification of omega-3 FAs in the diet, and the resulting effect on red cell membranes. Researchers found that this modification could significantly alter the FA ratio in cellular membranes, and subsequently alter the transport of glucose and insulin receptivity.

Insulin's function (analogous to a fuel injector in a car) is to drive the glucose (analogous to gasoline) into the cell (analogous to the car engine). To do this, insulin must overcome the cell membrane barrier. In our ancient ancestors, the cell membrane was composed of a 1:1 ratio of omega-6 to omega-3 FAs. However, now the cell membrane is composed of a ratio closer to 20:1 or 30:1. Thus, the insulin has greater difficulty in driving the glucose (fuel) into the cell (engine). The high composition of omega-6 FAs affects the structure of the cell membrane. As a result, the serum glucose levels remain high after consuming food, because of the cells' resistance to insulin. The body now registers higher levels of serum glucose than is homeostatically acceptable. As a result, the body produces more insulin to compensate for the higher serum glucose levels.

When we measure serum glucose levels early in this process, the glucose levels will register within the normal reference, giving both the clinician and patient a false sense of security. Unless the physiology is understood properly, the clinician will fail to recognize the development of insulin resistance, which is an early stage of type 2 diabetes.

In addition to the serum glucose level, an insulin level should be measured after an appropriate glucose load. This can be achieved by ingesting, 30 minutes prior to the serum insulin draw, eight ounces of orange juice and two white pieces of toast and jam. If the serum insulin level is above 20 ng/dl, 30 minutes after consuming the above, then insulin resistance is an issue that must be corrected.

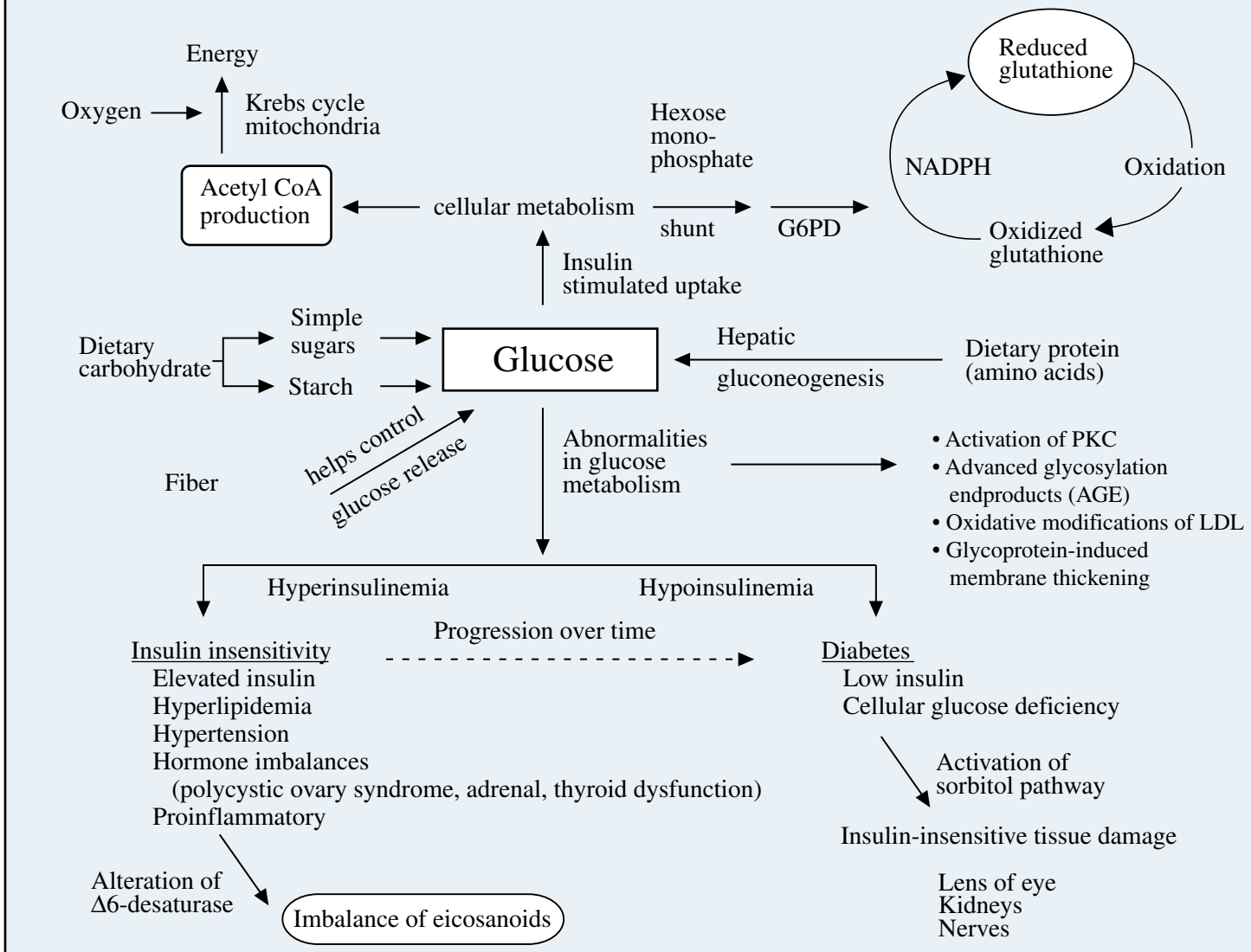
Potential consequences of insulin resistance

If insulin resistance is not recognized or corrected, and left to progress, the body will eventually maximize its production of insulin, until it can no longer compensate for the higher glucose levels. At this point, when the pancreas can no longer sustain its higher insulin output, the serum glucose values rise. Eventually, the clinician will initiate oral hypoglycemic drug therapy. This too will eventually fail and necessitate the use of insulin injection therapy to keep glucose levels within expectable measures.

Omega-3s and sugar levels

Failure to diagnose and treat insulin resistance leads to a gradual increase in the required dose of injectable insulin. Fortunately, supplemental omega-3 FAs can reverse insulin resistance due to increased omega-6 FA composition of the cell membrane. In fact, in patients who have required insulin injection therapy for years, glucose levels have dropped precipitously when omega-3 FA supplementation was started. Acute hypoglycemic events have resulted. This is easily corrected by decreasing the amount of insulin administered. It also offers further evidence that the omega-3 FAs sensitize the cell membrane to the effects of insulin.

Glucose Regulation and Functional Physiology



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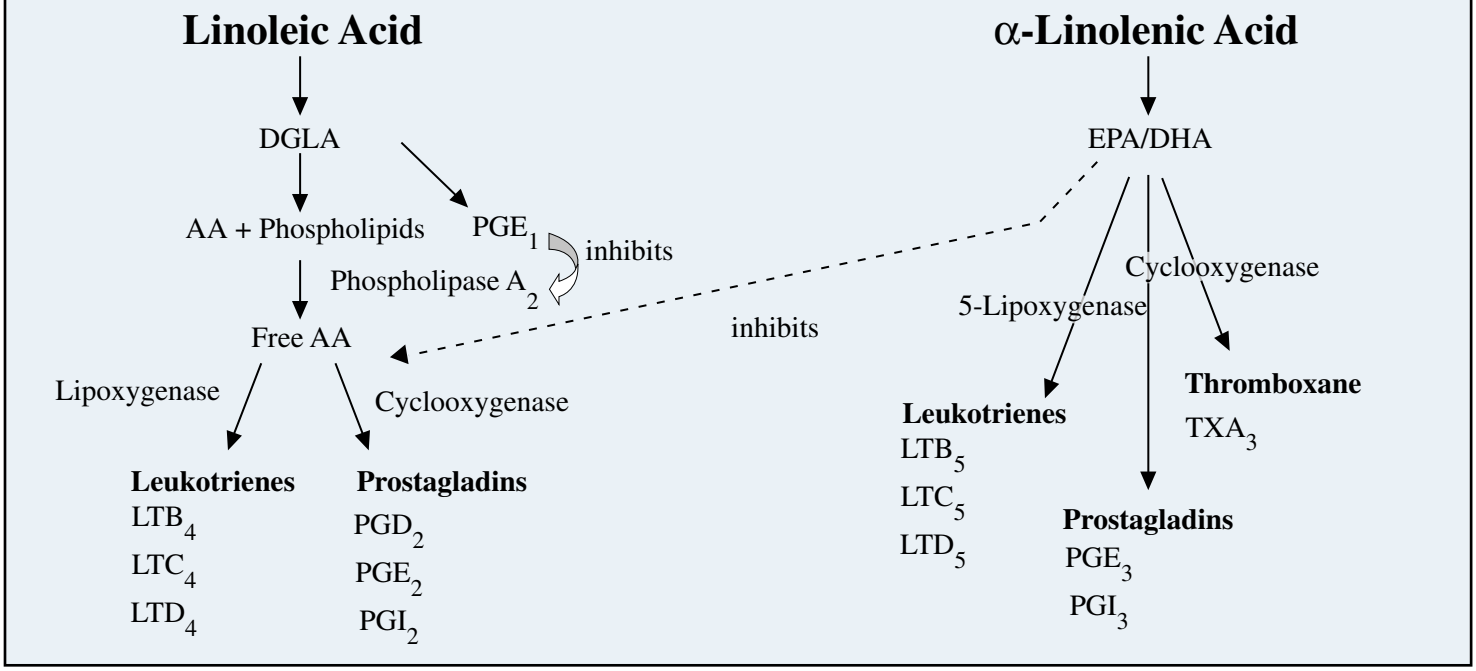
Role of Fatty Acids in Eicosanoid Production



In a side note, this author believes that the diagnosis of "hypoglycemia" is, in actuality, a hyper-insulinemic state caused by inadequate omega-3 FA consumption. It is also important to note that not all omega-3 FAs have been shown to increase cell membrane sensitivity to the effects of insulin. For example, supplementing omega-3 FAs from flaxseed oil did not increase the omega-3 FA in the phospholipid bilayer of cell membranes.

In addition to the contribution of EFAs to the physical structure of cell membranes, EFAs are involved in many regulatory processes. Over the last 25 years, advances in clinical nutrition, due to the efforts of scientists such as Horrobin, have suggested that EFA supplementation not only promotes glucose control in diabetic patients, but helps treat many other conditions, too. These include inflammation, compromised nerve conduction, neurological development, and vascular function.

Modulation of the inflammatory response

EFAs acts as precursors for the formation of eicosanoids, which include prostaglandins, thromboxanes, cytokines, and leukotrienes. These short-lived compounds, with autocrine and paracrine functions, are able to regulate numerous aspects of a cell's activity. Research has shown that eicosanoids are involved in an extraordinary number of physiological and pathological processes. These include, but are not limited to, inflammation, immune function, and vascular health.

Eicosanoids also appear to be involved in pathology associated with many degenerative diseases. One example is the cytokines (especially interleukin-1). Activated macrophages and T-lymphocytes release cytokines, which have been shown to both inhibit insulin secretion from the pancreatic beta cell, and induce beta cell degradation. The cellular mechanism responsible for the inhibition of the beta cells has been identified: Nitric oxide inactivates mitochondrial enzymes, which are produced during the inflammatory process. Figure 3 shows the pathways for the formation of various eicosanoids from their precursor fatty acids.

Many factors influence the complex production of prostaglandins and leukotrienes. These factors include the availability and type of fatty acids present in cellular membranes. It is not the purpose of this chapter to explain the actions of each individual eicosanoid. However, it is important to note the important physiologic actions exerted by eicosanoids, and the role that EFAs play in their regulation.

Defining inflammation

Inflammation is characterized by pain, redness, and swelling. These symptoms result from the presence of inflammatory mediators that enter a specific area. Important among inflammatory mediators are certain prostaglandins (PGE2); leukotrienes (LTB4), which are derived from AA metabolism; and the cytokines interleukin 1b (IL-1 b) and tumor necrosis factor a (TNF-a).

PGE2 contributes to the sensation of pain. LTB4 is a chemoattractant and activator of neutrophils, thereby enhancing the inflammatory response. IL-1 b and TNF-a also exert proinflammatory activity and directly contribute to inflammatory conditions.

Consumption of n-3 fatty acids suppresses the production of both TNF-a and IL-1 b. The result is amelioration of the inflammatory response. As a consequence, clinical trials are investigating the therapeutic use of omega-3 FAs with high EPA and DHA concentrations. Study results have been published on the impact of these n-3 fatty acids on inflammatory disorders such as irritable bowel syndrome, psoriasis and rheumatoid arthritis, to mention a few.

Exactly how n-3 fatty acids reduce these cytokines is not clear. It may be related to their ability to decrease thromboxane A2 (TXA2), a potent vasoconstrictor. Additionally, n-3 fatty acids help form LTB5, which stimulates significantly less of an inflammatory response than does LTB4, produced from AA metabolism.

Another possible explanation of how the inflammatory process is modulated involves the n-3 fatty acid's inhibitory effects on lipoxygenase. This effect decreases leukotrienes and cyclooxygenase, thereby reducing the pro-inflammatory two series prostaglandins. Both series two prostaglandins are derived from AA.

Omega-6 and inflammation

Given the effect of EFAs on inflammation, these fatty acids have found great utility in the treatment of rheumatologic conditions. Not only do n-3 fatty acids decrease proinflammatory mediators, certain n-6 fatty acids have a similar effect. The consumption of GLA-rich oil can increase dihomo-g-linolenic acid (DGLA, 20:3n-6). DGLA can be converted to series-1 prostaglandins (PGE1). PGE1 can reduce signs of inflammation such as pain and edema. DGLA can also inhibit the conversion of AA to proinflammatory leukotrienes, further reducing inflammation. Belch et al studied rheumatoid arthritis patients who took either evening primrose oil (540 mg GLA/d for 12 months) alone, or in combination with fish oil (240 mg EPA/d and 450 mg GLA/d). The patients' requirements for nonsteroidal anti-inflammatory drugs were significantly reduced. Zurier et al also found significant reductions in arthritis symptoms after treatment with GLA (2.8 g GLA/d).

In general, eicosanoids produced from the metabolism of AA tend to be proinflammatory, are more vasoconstrictive, favor platelet aggregation, and reduce immune responses. Those produced from DGLA and n-3 fatty acids tend to function in the opposite manner. Consequently, diets rich in EFAs can alter the production of eicosanoids toward those that favor decreased inflammatory responses, less platelet aggregation, and a more competent immune system, all of which are beneficial physiological responses.

EFAs and aging

The activity of the D-6 and D-5 desaturase enzymes (Fig. 1) are particularly important to the physiologic response to EFA consumption. While some studies have presented conflicting data, it is generally accepted that D6 and D5 desaturase activities decline with age. Consequently, as we age, the consumption of LA and ALA may have less of an impact on the production of other EFA metabolites.

Clinically, it is imperative to remember that in many aging patients, hyperinsulinemia can result from deregulation of insulin levels, due to dietary and lifestyle influences. The deregulation blocks D-6-desaturase activity and further depletes D-6-desaturase, preventing the conversion of ALA to EPA. Therefore, the consumption of EPA and GLA (both of which avoid the D-6 desaturase step) becomes increasingly important. Doses evaluated in studies for supplementation in diabetes (and hyperinsulinemia) are in the range of 100 mg GLA, 100 mg AA, 600 mg EPA, and 400 mg DHA.

EFAs and skin health

Atopic eczema is an excellent example of the importance of the D-6 desaturase. It has been known for years that EFAs are related to skin health, and that dermatitis is one of the first signs of EFA deficiency in both animals and humans. Hansen, who was a pediatrician and friend of Burr, observed that the dermatitis seen in EFA deficiency resembled the atopic eczema that he had observed in children. Hansen also observed that LA concentrations in eczema patients treated with LA were normal; however, AA levels were below normal.

It was not known at the time that LA is converted to AA in the body. However, Hansen discovered a defect in the metabolism of LA, specifically, a defect in D6 desaturase. Subsequently, numerous studies have now investigated the ability of GLA, which bypasses the D-6-desaturase step, to benefit those with atopic eczema. These studies have shown that supplementation with GLA can normalize cellular phospholipid composition, increase PGE2, and significantly improve symptoms such as itching. By using GLA to treat atopic eczema, steroid use can be reduced. Steroids are potentially harmful and do not address the underlying problem. It is unfortunate that more clinicians are not familiar with this research.

It is difficult to make specific recommendations for an optimal intake of EFAs. Over the past thousand years, the human diet has shifted to contain increasing amounts of n-6 fatty acids. Today, the average ratio of n-6 to n-3 fatty acids in the North American diet is at least 15:1. This is significantly different than the 1-4:1 ratio that characterized the Paleolithic diet.

Plants, specifically seed oils, provide rich source of PUFAs, usually of the n-6 family. For example, corn oil contains 52% of its

fatty acids as LA, 1% as ALA, and has an n6:n3 ratio of >50. In contrast, rapeseed oil (canola oil) contains 23% LA, 14% ALA, and an n6:n3 ratio of <2.

Most long-chain EFAs in the diet come from fish and fish oils. Atlantic cod contains 17% EPA and 38% DHA, while pink salmon contains 14% EPA and 19% DHA.

Given the different effects that n-6 and n-3 fatty acids have on important physiological functions, maintaining a balance of both types of EFAs is important. A diet high in EFAs results in a greater incorporation of these fatty acids in to cellular membranes, while simultaneously displacing AA. Consequently, less AA is available for conversion to harmful metabolites. This is of note, as diets high in EPA, DHA, and other EFAs have been correlated with beneficial health outcomes. These include reductions in the risk for developing atherosclerosis, osteoporosis, and depression.

Neurological importance of essential fatty acids

For years, EFAs have been known to affect the central nervous system. However, only recently have we begun to learn more about their functions with respect to the brain. The phospholipid fraction of the brain contains very little LA. Although AA is a dominant fatty acid in brain tissue, DHA is the major polyunsaturated fatty acid present.

The brain appears to require fatty acids with a high degree of unsaturation, and prefers DHA. In both adult and young animals, supplementation of various dietary oils can modulate brain levels of polyunsaturated fatty acids (PUFAs). Interestingly, it appears that of all the fatty acids, DHA can exert the most profound influence on brain PUFA levels. However, when animals are fed a diet deficient in DHA, a compensatory increase in docosapentaenoic acid (DPA, 22:5n-6), another highly unsaturated fatty acid, has been observed. This alteration can be reversed when the animals are again fed diets containing sufficient amounts of DHA.

These declines in brain DHA (but not in other tissues) are harder to achieve when an aged animal is fed a DHA-deficient diet. This further emphasizes the importance the body places on maintaining brain levels of DHA, even at the expense of other tissues. The exact mechanisms for why PUFAs are so important in the brain are not fully understood, but many relationships between DHA and EPA and brain function have been observed.

Shikano et al demonstrated that in vitro supplementation of cultured human eosinophilic leukemia cells with DHA resulted in a decrease in the platelet activating factor. It also reduced the activity of phospholipase A2 (PLA2). PLA2 is the key enzyme involved in the release of AA from membrane phospholipids, which allows AA to then be further metabolized to biologically active eicosanoids. If PLA2 activity is decreased, then less AA is available for the production of harmful metabolites.

DHA may also be involved in synaptic signal transduction. Jones et al reported that when radio-labeled DHA was given intravenously to rats, DHA was selectively incorporated into synaptic membrane phospholipids in response to cholinergic activation. This may indicate a role for DHA in phospholipid-mediated signal transduction at the synapse.

In addition to these cellular effects, behavioral effects related to brain function of PUFA supplementation have also been observed.

When rats were fed a high safflower oil diet, with an n-6:n-3 ratio of 75, approximately 90% less DHA was incorporated into phospholipids, compared with a soybean oil diet that contained an n-6:n-3 ratio of 7. Interestingly, rats fed the safflower oil diet exhibited less exploratory behavior, and did not perform as well in maze-learning tasks.

EFA deficiency and cognitive impairment

Simopoulos showed the significance of n-3 fatty acids in overall health, specifically in the areas of growth and development. Okuyama also demonstrated different behavioral patterns in rats fed a safflower oil diet, compared to rats fed n-3-rich perilla oil. Specifically, learning ability and retinal function were greater in the rats that consumed the perilla oil.

Changes in cognitive function are not limited to animal studies. Using data from the the Zutphen elderly study, Kalmijn found that n-3 PUFA consumption (mostly in the form of fish oil) was inversely correlated with cognitive decline and cognitive impairment. Moreover, it was reported that consumption of LA was positively associated with cognitive impairment.

Newman demonstrated that patients who died from Alzheimer's disease had an EFA deficiency, specifically, a DHA deficiency. He hypothesized that DHA deficiency compromises brain cell membranes. This allows the passage of an enzyme into the phospholipid bilayer membrane. The enzyme cuts beta amyloid precursor proteins away from cells at a critical intra-membrane position. As a result, a complete sequence of beta amyloid proteins is released into the extracellular space. The beta amyloid proteins appear to be the principal active constituents of senile plaque, believed cause brain damage in Alzheimer's disease.

EFAs and infants

The benefits of EFAs are not limited to adults. EFAs affect neurological changes beginning early in life, specifically during fetal and neonatal brain development. The fetus derives much of its EFAs from its mother's stores. Consequently, if these stores are not balanced, the potential for developmental abnormalities exists. In a study on rats, Green et al showed that PUFA levels plateau on the 17th embryonic day, while DHA levels continue to accumulate. This accumulation occurs just prior to synaptogenesis, again implicating DHA as a critical factor in synaptic functions.

It has also been shown that DHA is needed for glial cell development. Ikemoto et al demonstrated that DHA can directly promote neurite growth, whereas AA suppresses neurite growth.

Uauy-Dagach, et al demonstrated that DHA is needed for optimal development of visual function. Low birth-weight infants who were breast fed were compared to low birth-weight infants who were fed different commercial infant formulas. One formula was supplemented with marine oils to provide DHA. At 57 weeks, the breast-fed and DHA-supplemented infants had higher rod photoreceptor tests and better developed visual acuity.

SanGiovanni et al, at Harvard, conducted a meta-analysis of dietary EFAs and long-chain polyunsaturated FAs as they relate to visual resolution acuity in healthy pre-term infants. Stevens et al conclusively showed that 53 children who were diagnosed with attention-deficit hyperactivity disorder (ADHD) had significantly lower concentrations of key fatty acids in the plasma polar lipids as well as the red blood cell total lipids. They were compared to 43 control children who were not diagnosed with ADHD.

EFAs, dopamine, and serotonin

As discussed earlier, PUFAs play an important role in the physical properties of membranes. In fact, EFAs make up 45% of the fatty acids in synaptic membranes, and are critical to neuronal function. Consequently, the composition of EFAs in the synaptic membrane can influence the steps related to neurotransmitter synthesis, release, and overall activity.

In animals, n-3 fatty acid deficiency results in a decreased synthesis of dopamine and improper storage of newly synthesized dopamine. Monoamine oxidase can enzymatically degrade the poorly stored dopamine, resulting in a decreased availability of dopamine. EFA-deficient diets have also been observed to alter serotonergic functions. Delion et al reported an increase in the density of serotonin 2A receptors in animals fed diets deficient in n-3 fatty acids. It is therefore not unreasonable to associate n-3 fatty acid deficiency with the catecholaminergic changes seen in depression.

An inverse association has been observed, in middle-aged women, between the consumption of long-chain n-3 fatty acids and depression. Adams et al demonstrated an inverse correlation between plasma EPA and the severity of depression. They also reported an increased ratio of AA to EPA in depressed patients.

EFAs and brain health

These EFA changes could alter membrane function, and could therefore affect neurotransmitter systems. The exact reasons for the EFA abnormalities seen with depression are not known. However, it has been proposed that n-3 fatty acid metabolism may be altered in the presence of depression. The temporal relationship of this abnormality, with respect to depression (is it a cause or result), is still under investigation. However, in clinical practice, the benefits of n-3 fatty acids, in depression as well as other behavioral disorders and neurological development, has been clearly demonstrated.

Depression and psychological changes associated with dieting and weight cycling may also be related to alterations in EFA metabolism. Severe food restriction and very low-fat diets can induce changes in n-3 and n-6 fatty acid balance. Given the influence that these fatty acids can have on brain chemistry, extremely low-fat diets that alter EFA intake may have negative cognitive consequences.

Based on empirical findings, Yehuda et al suggest, among other things, that the critical factor in FA action and efficacy is not the absolute levels. Rather, it is the ratio between various groups of FAs acting as mediators of brain biochemistry and cognitive functions.

In an animal study using mice, Wainwright et al further demonstrated this idea. They found growth retardation in the offspring of female mice fed a diet with abnormal n-6 to n-3 ratio (0.32), but high DHA content compared with normal ratios (4.0).

Research has also uncovered the following:

- Uauy et al, while demonstrating the structural and functional role of EFAs in early life, determined that the most significant effects relate to neural development.
- Youdim et al showed that declining levels of PUFAs are associated with cognitive impairment and neurodegenerative disorders, such as Parkinson's and Alzheimer's.
- Fenton et al showed that deficient uptake or excessive breakdown of membrane phospholipids may be associated with schizophrenia.

Many other studies further support the role of balanced PUFAs and their role in behavior, cognitive function and neurological development.

Osteoporosis

When one thinks about EFAs, the topic of osteoporosis is not usually is not the first thing that comes to mind. However, the literature has identified a relationship between EFAs and bone metabolism, and that relationship has recently been gaining increased attention.

Soon after Burr and Burr identified EFAs, Borland and Jackson demonstrated that EFA-deficient animals developed calcified kidneys, due to a shift of calcium out of the bones. Unfortunately, this observation was not followed up with further research for approximately 20 years. It was then reported that EFA deficiency in animals can result in a loss of normal collagen and cartilage synthesis, as well as bone demineralization.

The streptozotocin-diabetic rat experiences significant hypercalcemia and has been used as a model to study the effect of EFAs on calcium metabolism. It is now understood that metabolites of both n-6 and n-3 fatty acids can reduce urinary calcium excretion.

Kruger and Horrobin, who postulated this, also noted that EFA-deficient animals developed severe osteoporosis, coupled with increased renal and arterial calcification. The authors point out that this calcification may be considerably more dangerous than the osteoporosis itself. Balanced n-6 and n-3 supplementation was noted to not only decrease urinary calcium excretion, but also to reduce ectopic calcifications and increase calcium deposition in bone. It was also observed to increase calcium absorption from the gut.

The mechanism by which EFAs alter calcium excretion needs to be further clarified. However, many researchers have shown that PGE2 increases urinary calcium excretion, and inhibition of PGE2 levels can reduce calcium losses. Since PGE2 production results from AA metabolism, a favorable balance of n-3 and n-6 fatty acids should positively effect calcium excretion.

Buck et al reported such a finding, demonstrating that a combination of n-6 and n-3 fatty acids significantly decreased urinary calcium. As previously mentioned, EFAs have also been shown to affect calcium absorption from the gastrointestinal tract, as there is a close relationship between calcium transport, EFAs, and vitamin D.

Van Dokkum et al demonstrated that EFA supplementation in humans reduced fecal calcium losses and stimulated calcium absorption from the gut. Using radioisotopes, Buck et al reported that supplementation with either fish oil, evening primrose oil, or a combination of the two, significant increased calcium absorption. It has been hypothesized that changes in membrane composition, due to EFA supplementation, may alter ion pump activity or ion channel function. That, in turn, enhances the intestinal response to vitamin D.

EFAs are also able to affect bone metabolism. While beyond the scope of this discussion, it is well known that prostagladins influence bone metabolism. Given the ability of EFAs to influence prostaglandin formation, EFAs may have potent bone-stimulating actions. Watkins et al demonstrated in animals that EPA supplementation can stimulate bone formation in association with reduced amounts of PGE2.

Van Papendorp et al supplemented osteoporotic women with evening primrose oil, fish oil, a combination of the two, or olive oil, for 16 weeks. Alkaline phosphatase was significantly decreased, while osteocalcin levels increased in the group receiving fish oil, and in the group receiving a combination of fish oil and evening primrose oil.

Additionally, Kruger et al supplemented women with calcium, in combination with GLA and EPA or a placebo, for 18 months. Women who received the EFAs and calcium showed improvements in femoral and lumbar bone density, while those receiving a placebo did not.

Das further discusses the significant role of EFA supplementation in preventing osteoporosis in postmenopausal women. Given the amount of work that has been done on eicosanoids and their effect on bone metabolism, and our knowledge on the effect of EFAs on eicosanoid metabolism, it is unfortunate that the area of EFAs and bone health has not been further expanded.

The future: Beyond EFA supplementation

EFAs and their imperative role in health and development are well recognized among many scientists and clinicians today. However, they have not drawn the interest of the majority of the medical community, as they justifiably warrant.

The limited space in this chapter allows us just a brief glimpse of how significant EFAs, especially of the n-3 variety, are to our overall health and well being. The range of health conditions and disorders resulting from EFA deficiencies is virtually endless. Referenced journal articles and studies on EFAs, in just the first 100 of over 900 references found, ranged the entire gamut of medicine. They included the role of EFAs in deficiency states, hepatic function, alcohol metabolism, bone density, developmental delays, neurologically disabilities, hypertension, acute respiratory distress syndrome (ARDS), vision impairment, fertility, maternal nutrition and health, breast milk, neonatal nutrition and development, structural and functional role in normal development, hormonal responses, and bronchial asthma. EFA deficiencies are also involved in impaired glucose metabolism, insulin resistance, NIDDM, IDDM, gastrointestinal absorption and digestion, altered gastrointestinal function, blepharospasm, and multiple sclerosis (MS). Furthermore, they are believed to contribute to effects in various types of cancer, cytotoxicity to cancer cell lines, schizophrenia and other behavioral problems, addictive personalities, and depression. In addition, EFA decifits are associated with cardiovascular conditions, glioma, malaria, cigarettes and metabolism, drug resistance, eclampsia, obesity, aging, peptic ulcer disease, degenerative joint disease, dermatological conditions, chronic fatigue, renal impairment, systemic lupus, cystic fibrosis, and exercise metabolism. They are also linked to impaired immune function, anti-bacterial action, insomnia, lipid metabolism, neuropathy, and decubidus ulcers, just to name a few.

EFAs as mode of transport

The subject of EFAs goes far beyond that of supplementation in diet and utilization in deficiency states. A relatively uncharted area of science utilizes EFAs as a mechanical means of therapy, such as employment in a drug delivery system. Already, EFAs have been effectively used as the mode of transport for a number of unique, experimental treatment modalities. These include B-lymphocyte stimulators, as well as growth hormone-releasing hormone analogs, which use polypeptide synthesis technologies far more advanced than the solid state synthesis or polymerase units.

Traditional drug delivery mechanisms have been ineffective with these polypeptide structures. Their sensitive nature results in actions analogous to hormones. Because of their fragility, these polypeptide sequences are susceptible to denaturing by the gastrointestinal acids and enzymes. In addition, our modern-day lifestyle has created a tremendous vacillation in gut function and poor gut absorption. These factors also prevent oral delivery mechanism from being a viable option. Conventional paraenteral routes (IV, IM or SQ injections) raise the issues of compliance and convenience, due to the necessity for daily injections.

Utilizing specific combinations of EFAs with other carrier substances, these new polypeptide treatment modalities now have a way of being delivered into the system in a trans-dermal manner without the concerns of denaturing or issues regarding compliance. Furthermore, not only do these EFA trans-dermal transport delivery mechanisms allow for convenient dosing, but are reported to actually contribute to stabilizing the polypeptide structures. Not surprisingly, assimilation into the system is also achieved beyond that of other delivery mechanisms including other non-EFA trans-dermal delivery mechanisms.

Final thoughts

The therapeutic potential of EFAs in all fields of medicine has been definitively established. For example, we now recognize that enzyme deficiencies, such as those observed with D-6-desaturase, decrease the synthesis of n-6 and n-3 PUFAs. In addition, these enzyme deficiencies may be particularly important in the actual process of aging, where D-6-desaturase activity is already impaired.

We need to learn how EFAs can be advanced beyond simple supplementation, and utilized in therapeutic modalities. New discoveries about EFAs promise to advance the field of longevity medicine, not only by increasing the life span of our future generations, but by improving the quality of that increased life.

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