Biological Significance of Essential Fatty Acids

UN Das

Abstract

Essential fatty acids (EFAs) - linoleic acid (LA) and α-linolenic acid (ALA) are critical for human survival. EFAs are readily available in the diet. But, to derive their full benefit, EFAs need to be metabolized to their respective long-chain metabolites. EFAs not only form precursors to respective prostaglandins (PGs), thromboxanes (TXs), and leukotrienes (LTs), but also give rise to lipoxins (LXs), resolvins, isoprostanes, and hydroxy- and hydroperoxyeicosatetraenoates. Certain PGs, TXs, and LTs have pro-inflammatory actions whereas LXs and resolvins are anti-inflammatory in nature. Furthermore, EFAs and their long-chain metabolites modulate the activities of angiotensin converting and HMG-CoA reductase enzymes, enhance acetylcholine levels in the brain, increase the synthesis of endothelial nitric oxide, augment diuresis, and enhance insulin action. Thus, EFAs and their metabolites may function as endogenous ACE and HMG-CoA reductase inhibitors, nitric oxide enhancers, β-blockers, diuretics, anti-hypertensive, and anti-atherosclerotic molecules. In addition, EFAs and their long-chain metabolites react with nitric oxide (NO) to yield respective nitroalkene derivatives that exert cell-signaling actions via ligation and activation of peroxisome proliferator-activated receptors (PPARs). Thus, EFAs and their derivatives have varied biological actions that may have relevance to their involvement in several physiological and pathological processes.

INTRODUCTION

Essential fatty acids (EFAs) are essential for survival of humans and other mammals and they cannot be synthesized in the body and hence, have to be obtained in our diet and thus, are essential. EFAs form an important constituent of all cell membranes, and confer on membranes properties of fluidity and thus, determine and influence the behaviour of membrane-bound enzymes and receptors. There are two types of naturally occurring EFAs in the body, the ω-6 series derived from linoleic acid (LA, 18:2) and the ω-3 series derived from α-linolenic acid (ALA, 18:3). Both ω-6, and ω-3 series of unsaturated fatty acids are metabolized by the same set of enzymes to their respective long-chain metabolites. While some of the functions of EFAs require their conversion to eicosanoids and other products, in majority of the instances the fatty acids themselves are active. The longer chain metabolites of LA and ALA are important in regulating membrane function, and are of major importance in the brain, retina, liver, kidney, adrenal glands and gonads.

Metabolism of essential fatty acids

EFAs are also called as polyunsaturated fatty acids (PUFAs) since they contain two or more double bonds. PUFAs are fatty acids some of which have at least two carbon-to-carbon double bonds in a hydrophobic hydrocarbon chain. There are at least four independent families of PUFAs, depending on the parent fatty acid from which they are synthesized. They include:

- The “ω-3” series derived from α-linolenic acid (ALA, 18:3, ω-3).
- The “ω-6” series derived from cis-linoleic acid (LA, 18:2, ω-6).
- The “ω-9” series derived from oleic acid (OA, 18:1, ω-9).
- The “ω-7” series derived from palmitoleic acid (PA, 16:1, ω-7).

LA is converted to γ-linolenic acid (GLA, 18:3, n-6) by the action of the enzyme Δ⁶ desaturase (d-6-d) and GLA is elongated to form dihomo-GLA (DGLA, 20:3, n-6), the precursor of the 1 series of prostaglandins (PGs). DGLA can also be converted to arachidonic acid (AA, 20:4, n-6) by the action of the enzyme Δ⁵ desaturase (d-5-d). AA forms the precursor of 2 series of prostaglandins, thromboxanes and the 4 series of leukotrienes. ALA is converted to eicosapentaenoic acid (EPA, 20:5, n-3) by d-6-d and d-5-d. EPA forms the precursor of the 3 series of prostaglandins and the 5 series of leukotrienes. LA, GLA, DGLA, AA, ALA, EPA and docosahexaenoic acid (DHA, 22:6, n-3) are all PUFAs, but only LA and ALA are EFAs (see Fig. 1 for metabolism of EFAs). AA and EPA...
also give rise to their respective hydroxy acids, which in turn are converted to their respective leukotrienes (LTs). In addition, AA, EPA, and DHA also give rise to certain anti-inflammatory compounds such as lipoxins and resolvins that have potent anti-inflammatory actions. PGs, LTs, lipoxins (LXs), and resolvins are highly active, modulate inflammation, and are involved in various pathological processes such as atherosclerosis, bronchial asthma, inflammatory bowel disease, and other inflammatory conditions.3-8 In the present discussion, the term “EFAs” is used to refer to all unsaturated fatty acids: LA, GLA, DGLA, AA, ALA, EPA, and DHA; and the term polyunsaturated fatty acids (PUFAs) refers to GLA, DGLA, AA, EPA, and DHA. Although the terms EFAs and PUFAs are used interchangeably for the sake of convenience it should be understood that all EFAs are PUFAs but all PUFAs are not EFAs. It should be noted that many of the functions of EFAs are also brought about by PUFAs and EFA-deficiency states can be corrected to a large extent by PUFAs. This led to the suggestion that PUFAs are “functional EFAs”. Hence, in general, many authors use the terms EFAs and PUFAs interchangeably. This convention is followed in the present discussion also.

EFAs/PUFAs play a significant role in the pathobiology of clinical conditions such as collagen vascular diseases, hypertension, diabetes mellitus, metabolic syndrome X, psoriasis, eczema, atopic dermatitis, coronary heart disease, atherosclerosis, and cancer.3-8 This is in addition to the role of PGs and LTs in these conditions. For instance, in bronchial asthma the inflammatory events are initiated and perpetuated by PGs and LTs produced from AA, whereas when significant amounts of EPA and DHA are given the inflammatory process is abrogated to a large extent. This beneficial action of EPA/DHA when supplemented from external sources has been attributed to the displacement AA from the cell membrane phospholipid pool and to the formation of less pro-inflammatory PGs and LTs from them, and anti-inflammatory molecules LXs and resolvins and hence the favourable response. If the molecular mechanism(s) by which various stimuli are able to preferentially induce the release of AA, EPA and/or DHA and convert them to their respective products, then it is possible to develop methods or strategies to treat various inflammatory conditions based on this knowledge. This is so, since armed with such knowledge one will be able to preferentially divert the formation of less pro-inflammatory molecules from EPA/DHA. Since LXs and resolvins resolve inflammation by suppressing leukocyte infiltration and clearance of the cellular debris from the site of inflammation, it is relevant to know how their formation is regulated in the cells and tissues and in various diseases. Thus, PUFAs form precursors to both pro- and anti-inflammatory molecules and the balance between these mutually antagonistic compounds could determine the final outcome of the disease process.

Sources of EFAs

EFAs: LA and ALA are present in human diet in abundant amounts and hence, EFA-deficiency is uncommon. In certain specific conditions such as total parental nutrition (TPN) and severe malabsorption occasionally EFA deficiency could be seen. The present TPN solutions contain adequate amounts of EFAs. The manifestations of EFA deficiency include: dry and scaly skin, hepatosplenomegaly, immunodeficiency, inappropriate water loss through the skin, dehydration, scalp dermatitis, alopecia, and depigmentation of hair.6,10 EFAs are widely distributed in normal human diet. The main dietary sources of EFAs are as follows.

All PUFAs are present in human breast milk that explains why breast-fed children are healthier compared to bottle-fed. LA and ALA are present in significant amounts in dairy products, organ meats such as liver, and many vegetable oils such as sunflower, safflower, corn and soy. GLA is present in evening primrose oil at concentrations of 7-14% of total fatty acids; in borage seed oil it is 20-27%; and in black currant seed oil at 15-20%. GLA is also found in some fungal sources.12 DGLA is found in liver, testes, adrenals, and kidneys. AA is present in meat, egg yolks, some seaweeds, and some shrimps. Average daily intake of AA is estimated to be in the region of 100-200 mg/day, more than enough to account for the total daily production of various PGs.

EPA and DHA are present mainly in marine fish. Fresh water fish are unlikely to contain substantial amounts of EPA and DHA. Cow’s milk contains very small amounts of GLA, DGLA and AA.

Since EFAs/PUFAs are unstable due to the presence of two or more double bonds in their structure, substantial loss occurs during food processing and hydrogenation of oils. Exposure to high temperatures and during hydrogenation, EFAs/PUFAs are denatured and converted into trans fats that are harmful to the body.13-15 It is generally believed that the fall in the intake of ω-3 fatty acids EPA and DHA in the last 50 years is responsible for the increasing incidence of atherosclerosis, CHD, hypertension, metabolic syndrome X, obesity, collagen vascular diseases and possibly, cancer.

Modulation of metabolism of EFAs

Dietary LA and ALA are metabolized by the same set of Δ6 and Δ5 desaturases and elongases to their respective metabolites (Fig. 1). As a result, these two fatty acids compete with one another for the same set of enzymes. Δ6 and Δ5 desaturases prefer ω-3 to ω-6. Oleic acid (OA, ω-9) that is not an EFA is also metabolized by the same Δ6 and Δ5 desaturases. But, in view of the preference of these enzymes to LA and ALA, under normal physiological conditions, the metabolites of ω-9 are
formed only in trivial amounts. Hence, presence of significant amounts of 20:3 \( \omega-9 \), a metabolite of OA, in the cells and plasma suggests that there is EFA deficiency.

Several factors influence the activities of desaturases and elongases.\(^1,2,12,16,17\) Saturated fats, cholesterol, trans-fatty acids, alcohol, adrenaline, and glucocorticoids inhibit \( \Delta^6 \) and \( \Delta^5 \) desaturases. Pyridoxine, zinc, and magnesium are necessary co-factors for normal \( \Delta^6 \) desaturase activity. Insulin activates \( \Delta^6 \) desaturase whereas diabetics have reduced \( \Delta^6 \) desaturase activity. The activity of \( \Delta^6 \) desaturase falls with age. Oncogenic viruses and radiation inhibit \( \Delta^6 \) desaturase. Total fasting, protein deficiency, glucose rich diets reduce the activity of \( \Delta^6 \) desaturase. A fat-free diet and partial caloric restriction enhances \( \Delta^6 \) desaturase. Activities of \( \Delta^6 \) and \( \Delta^5 \) desaturases are decreased in diabetes mellitus, hypertension, hyperlipidemia, and metabolic syndrome X. Trans fats, saturated fatty acids, and cholesterol interfere with EFA metabolism and promote inflammation, atherosclerosis and coronary heart disease.\(^14,15,17\) This suggests that trans fats, saturated fats, and cholesterol have pro-inflammatory actions whereas EFAs and PUFAs possess anti-inflammatory properties.

### Actions of EFAs/PUFAs

#### Cell membrane fluidity

Cell membrane fluidity is determined by its lipid composition, and increased incorporation of saturated fatty acids and cholesterol into the membrane phospholipids will make them rigid. In contrast, increased incorporation of unsaturated fatty acids into the membrane will make it more fluid, increase the number of receptors, and their affinity to their respective hormones or growth factors. For example, increase in the rigidity of the cell membrane reduces the number of insulin receptors and their affinity to insulin that, in turn, causes insulin resistance. In contrast, increase in cell membrane fluidity due to increase in the unsaturated fatty acid content in the membrane phospholipids, increases the number of insulin receptors and their affinity to insulin and thus, decreases insulin resistance.\(^18\) The growth and development of brain during the perinatal period and adolescence is dependent on the availability of \( \omega-3 \) and \( \omega-6 \) fatty acids.\(^19-21\) Hence, decreased availability of \( \omega-3 \) and \( \omega-6 \) fatty acids during this critical period of growth may impair brain growth and the development of appropriate synaptic connections that, in turn, may lead to the development neuropsychological conditions such as dementia, depression, schizophrenia, Alzheimer’s disease, and neurodegenerative diseases: Huntington’s disease, Parkinson’s disease, spinocerebellar degeneration, etc.

#### Second messenger action

EFAs and their metabolites including eicosanoids have second messenger like actions. Several hormones and growth factors activate phospholipase A\(_2\) (PLA\(_2\) that, in turn, induces the release of DGLA, AA, \( \text{EPA} \), and DHA from the cell membrane lipid pool. These fatty acids are utilized for the formation of various eicosanoids and bring about their actions. Inhibition of PLA\(_2\) interferes with the action of several growth factors and cytokines. For example, the tumoricidal action of TNF-\( \alpha \) is dependent on its ability to induce PLA\(_2\) and inhibitors of PLA\(_2\) completely blocked its (TNF-\( \alpha \)) anti-cancer action. PUFAs enhance the activity of protein kinase C (PKC), a well-known second messenger, activate macrophages and polymorphonuclear leukocytes (PMNs) and increase free radical generation.\(^1,2,8\)

#### Anti-bacterial, anti-viral, and anti-fungal actions of EFAs

LA rapidly killed cultures of \textit{Staphylococcus aureus}, and hydrolyzed linseed oil (which contains both LA and ALA) inactivated methicillin-resistant \textit{S. aureus}. PUFAs inactivated enveloped viruses and showed anti-fungal properties.\(^22-24\)

### PUFAs inhibit ACE and HMG-CoA reductase activities and augment endothelial nitric oxide generation

PUFAs inhibited leukocyte ACE activity\(^25\) and enhanced endothelial nitric oxide (eNO) generation.\(^26\) These results indicate that PUFAs regulate ACE activity formation of Ang-II. This implies that when tissue
concentrations of PUFAs are low, the activity of ACE will be high resulting in increased formation of angiotensin-II and a simultaneous decrease in eNO.

Transgenic rats overexpressing human renin and angiotensinogens genes (dTGR) develop hypertension, inflammation, and renal failure. These animals also showed specific renal P450-dependent AA metabolism changes that led to decreased formation epoxyeicosatrienoic acids (5,6-, 8,9-, 11,12- and 14,15-EETs) and hydroxyeicosatetraenoic acids (19- and 20-HETEs) as a result of microsomal decrease of AA epoxygenases and hydroxylases. Both EETs and HETEs are potent inhibitors of IL-6 and TNF-α-induced activation of NF-kB and prevent vascular inflammation. These results suggest that AA and other PUFAs not only regulate ACE activity and Ang-II levels in the tissues but also possess anti-inflammatory properties by generating certain anti-inflammatory metabolites.

PUFAs, especially EPA and AA, stimulate eNO synthesis\(^{6,8,26}\) that may explain their anti-atherosclerotic and anti-inflammatory actions. Aspirin enhances the formation of eNO through the generation of epi-lipoxins, which possess anti-inflammatory action.\(^{28}\) Aspirin acetylates the active site of the inducible cyclo-oxygenase (COX-2) to generate epi-lipoxins, lipoxins and resolvins from AA, EPA, and DHA that, in turn, induce the production of eNO. NO not only blocks the interaction between leukocytes and the vascular endothelium during inflammation but also stimulates the formation of PGL, a potent vasodilator and platelet anti-aggregator, from AA.\(^{29,30}\) In addition, aspirin inhibits the formation of TXA, a potent platelet aggregator and vasoconstrictor, and thus, tilts the balance more in favour of platelet anti-aggregators and vasodilators NO and PGL.\(^{1}\)

PUFAs are potent inhibitors of the HMG-CoA reductase enzyme and similar to statins are useful in the treatment of hyperlipidemias, and bind to DNA and regulate the expression of genes and oncogenes.\(^{31-35}\) Statins, in turn, enhance plasma AA levels and decrease the ratio of EPA to AA significantly.\(^{32}\) This suggests that PUFAs mediate many actions of statins\(^{46}\) and this could be one mechanism by which they lower cholesterol levels. Statins and PUFAs have many overlap actions such as inhibition of IL-6 and TNF-α production and NF-kB activation; and thus, possess anti-inflammatory actions and both are useful in atherosclerosis, coronary heart disease, osteoporosis, stroke, Alzheimer’s disease, and inflammatory conditions such as lupus and cancer.\(^{26,36-54}\) These similar and overlap actions strongly indicate that the molecular mechanisms of actions of statins and PUFAs are similar, if not identical. Furthermore, when a combination of statins and PUFAs are given together a synergistic beneficial effect was seen in patients with combined hyperlipemia.\(^{55}\)

HMG-CoA reductase enzyme catalyzes the synthesis of mevalonate, which is the rate-limiting step in the mevalonate pathway. Mevalonate is the precursor of cholesterol and a variety of isoprenoid-containing compounds. These isoprenoid precursors are necessary for the posttranslational lipid modification (prenylation) and hence, the function of Ras and other small GTPases. Inhibition of mevalonate pathway disrupts the function of oncogenic forms of Ras, which is necessary for cell proliferation. Thus, both statins and PUFAs suppress Ras activity, show anti-proliferative action and induce apoptosis of tumor cells.\(^{56,57}\) Furthermore, small GTPases, the prenylated products of the mevalonate pathway, have negative control on the expression of BMPs (bone morphogenetic proteins). Both PUFAs and statins prevent the function of small GTPases and enhance the expression of various BMPs by their ability to inhibit the mevalonate pathway. BMPs are known to be essential for neuronal growth, proliferation, and differentiation,\(^{38}\) and also for bone growth.\(^{41}\) Thus, PUFAs modulate brain growth and development, and neuronal differentiation. This beneficial action is in addition to their (PUFAs) ability to form an important constituent of neuronal cell membranes and involve in memory formation and consolidation.\(^{19-21}\) This explains why PUFAs are useful in the prevention and treatment of dementia and Alzheimer’s disease.\(^{52,53,59}\) Similar to PUFAs, statins also enhance the concentrations of BMPs in brain and bone and thus could be of benefit in the treatment of Alzheimer’s disease and osteoporosis,\(^{41,42}\) though this has been disputed. Yet another action of PUFAs and statins that contributes to their beneficial actions is their ability to enhance eNO,\(^{26,60}\) a pleiotropic molecule that has many biological actions including its ability to function as a neurotransmitter\(^{61}\) and prevent osteoporosis.\(^{52,63}\) But the major difference between PUFAs and statins is the fact that statins cannot be given confidently during pregnancy, lactation and infancy for the fear of fetal toxicity and teratogenesis,\(^{54}\) whereas PUFAs can be given any time during the lifespan with no side effects. In fact, PUFAs are recommended during pregnancy and lactation and infancy to improve brain growth and development.\(^{19,22}\) Furthermore, PUFAs are natural endogenous substances.

**PUFAs inhibit the synthesis of pro-inflammatory cytokines**

AA, EPA, and DHA; Lxs and resolvins suppress IL-1, IL-2, IL-6, and TNF-α production by T cells.\(^{55-57}\) This suggests that EFAs/PUFAs and their metabolites function as endogenous anti-inflammatory molecules and regulate immune response. IL-1, IL-6, and TNF-α induce insulin resistance\(^{68,69}\) and have cytotoxic and neurotoxic actions.\(^{70}\) Cachexia seen in patients with chronic diseases such as tuberculosis, cancer, and AIDS is due to excess production of TNF-α and other pro-inflammatory cytokines.\(^{71,72}\) EPA, and other PUFAs ameliorate cachexia to some extent induced by TNF-α.\(^{73}\)
Several retroviral agents induced lipodystrophy and insulin resistance could be due to increased levels of TNF-α and decreased concentrations of adiponectin.\textsuperscript{77} PUFAs by decreasing TNF-α levels and enhancing adiponectin levels prevent/reverse insulin resistance, if given sufficiently early in the disease process.\textsuperscript{79-82}

Some of the beneficial actions of PUFAs in various inflammatory conditions are due to the formation of anti-inflammatory compounds such as lipoxins, resolvins, and neuroprotectin D1. Hence, a brief review of these molecules is in place here.

**Lipoxins, resolvins, and neuroprotectin D1 from EFAs/PUFAs**

Aspirin converts AA, EPA and DHA to 15 epimer LXs (ATLs) that are potent inhibitors of acute inflammation by utilizing the COX-2 enzyme due to the close interaction between endothelial cells and PMNs. In situation wherein there is a deficiency of LXs, interaction between PMN-endothelial cells occurs leading to endothelial damage that may result in the development and progression of atherosclerosis, thrombus formation and coronary artery disease, and persistence of inflammation.

Murine brain cells expressing COX-2, when treated with aspirin, transformed enzymatically DHA to 17R series of hydroxy DHAs (HDHAs) that, in turn, is converted enzymatically by PMNs to di- and tri-hydroxy containing docosanoids. Similar small molecular weight compounds (similar to HDHAs) are generated from AA and EPA. Thus, 15R-hydroxy containing compounds are formed from AA, 18R series from EPA, and 17R-hydroxy series from DHA. All these compounds have potent anti-inflammatory actions and have been termed as “resolvins” (see Figure 1). Resolvins inhibited cytokine generation, leukocyte recruitment, leukocyte diapedesis, and exudate formation. AA, EPA, and DHA-derived resolvins from acetylated COX-2 are formed via transcellular biosynthesis (e.g. due to cell-cell communication between endothelial cells and PMNs). Resolvins inhibit brain ischemia-reperfusion injury. Thus, lipoxins and resolvins formed from AA, EPA, and DHA have cardioprotective, neuroprotective, and other cytoprotective actions.\textsuperscript{83,84}

Of the several 17-hydroxy-containing bioactive mediators derived from DHA that were termed docosatrienes and 17S series resolvins, 10,17S-dihydroxydocosatriene termed as neuroprotectin D1 (NPD1) reduced the infiltration of PMNs, showed anti-inflammatory and neuroprotective properties,\textsuperscript{52,85} and inhibited oxidative stress.\textsuperscript{86} Both LXs and NPD1 enhanced wound healing,\textsuperscript{87} and promoted brain cell survival.

It is likely that under physiological conditions, both COX-1 and COX-2 enzymes are utilized for the formation of beneficial eicosanoids such as PGE\textsubscript{1}, PGI\textsubscript{2}, and LXs, resolvins, and NPD1 so that inflammation is prevented/restricted/resolved. Failure to produce adequate amounts of LXs, resolvins, and NPD1 or interference with their action and a simultaneous increase in the production of pro-inflammatory PGs, TXs, and LTs, and cytokines could lead to initiation and persistence of inflammation and tissue damage.

**EFAs in various pathological processes**

**Inflammation**

PUFAs and their products play a significant role in inflammation. The amount and type of PUFAs released in response to inflammatory stimuli depends on the cell membrane phospholipid fatty acid content. Since EFAs have to be obtained from diet, it suggests that dietary content of EFAs is one factor that modulates the degree of inflammation. Increased dietary intake of GLA, DGLA, and EPA/DHA substantially decreases inflammatory response.\textsuperscript{89} This beneficial action can be ascribed to decreased formation of pro-inflammatory eicosanoids and cytokines, and an increase in the production of beneficial molecules such as PGE\textsubscript{1}, PGI\textsubscript{2}, PGI\textsubscript{3}, HPETEs, eNO, LXs, resolvins and NPD1. It is known that when the cell membrane lipid pool is rich in GLA/DGLA/EPA/DHA and contains appropriate amounts of AA, there could occur specific activation of sPLA\textsubscript{2} and cPLA\textsubscript{2} (soluble and cytosolic phospholipase A\textsubscript{2} respectively) in response to an injury/inflammatory stimuli that leads to the formation of increased amounts of LXs, PGD\textsubscript{2} and 15deoxy Δ\textsuperscript{12-14}PGJ\textsubscript{2}, eNO, GSNO, PGE\textsubscript{1}, PGI\textsubscript{2}, PGI\textsubscript{3}, and HPETEs that dampen inflammatory process and enhance resolution of inflammation. It was demonstrated that exogenous PUFAs preferentially activate type IIa sPLA\textsubscript{2}-mediated AA release from IL-1 stimulated cells and this, in turn, led to the formation of anti-inflammatory LXs, PGD\textsubscript{2}, and 15deoxy Δ\textsuperscript{12-14}PGJ\textsubscript{2}, resulting in the prevention and resolution of inflammation.\textsuperscript{88,89} Several studies showed that oral or parenteral supplementation of GLA/EPA/DHA is of benefit to patients with rheumatoid arthritis, lupus, psoriasis, sepsis, inflammatory bowel disease, nephritis, bronchial asthma, dermatitis, and in other inflammatory conditions (reviewed in 1-5, 8, 12, 58, 59).

**Atherosclerosis**

Healthy endothelial cells synthesize and release adequate amounts of NO, PGI\textsubscript{2}, and PGE\textsubscript{1}, to prevent aggregation of platelets so that atherosclerosis would not occur. Pro-inflammatory cytokines such as IL-1, IL-2, IL-6, and TNF-α induce oxidant stress by enhancing the production of free radicals by monocytes, macrophages, and leukocytes. Increased production of pro-inflammatory cytokines and free radicals occurs due to shear stress, hyperglycemia, clinical or sub-clinical infections, and low-grade systemic inflammation as seen in type 2 diabetes mellitus, hypertension,

© JAPI • VOL. 54 • APRIL 2006 www.japi.org 313
hyperlipidemia, and metabolic syndrome X. EPA/DHA/AA and HDL inhibit free radical generation, suppress IL-6 and TNF-α synthesis and secretion, enhance eNOSynthesis, and thus, prevent oxidant stress [reviewed in 90]. PUFAs may also enhance HDL levels. These evidences suggest that endothelial cell deficiency of PUFAs increases the production of pro-inflammatory cytokines and free radicals that results in the development of insulin resistance; decrease in plasma and cellular HDL concentrations, and decrease the formation of eNO, PGE1, PGI2, PGI3, LXs, resolvins, and NPD1 that may ultimately promote atherosclerosis. Providing adequate amounts of various PUFAs can restore normalcy.90

Metabolic syndrome X

Plasma levels of C-reactive protein (CRP), TNF-α, and IL-6, markers of inflammation, are elevated in subjects with obesity, insulin resistance, essential hypertension, type 2 diabetes, and CHD. Higher plasma CRP concentration is associated with increased risk of CHD, ischemic stroke, peripheral arterial disease, and ischemic heart disease mortality in healthy men and women. Similarly, a strong correlation exists between elevated CRP levels and cardiovascular risk factors, fibrinogen, and HDL cholesterol. IL-6, a pro-inflammatory cytokine stimulates the production of CRP in the liver. In overweight and obese subjects, serum levels of TNF-α were significantly higher compared to lean subjects. Weight reduction or regular exercise decreases serum concentrations of TNF-α. A negative correlation exists between plasma TNF-α and HDL cholesterol, glycosylated hemoglobin, and serum insulin concentrations. These evidences suggest that metabolic syndrome X can be considered as a low-grade systemic inflammatory condition.91

EPA, DHA, and AA, inhibit TNF-α and IL-6 production,66 enhance eNOS generation,26 inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase31,32 and angiotensin converting enzyme activities,25 function as endogenous ligands for PPARs,92 suppress leptin gene expression,39 enhance the production of adiponectin,82 and decrease insulin resistant.79,80 This may explain why PUFAs are useful to protect against CHD, prevent the progression of atherosclerosis, and decrease blood pressure. Furthermore, decreased concentrations of EPA, DHA and AA in skeletal muscle phospholipids were found to be associated with decreased insulin sensitivity in humans.84 I observed that plasma phospholipid concentrations of EPA, DHA and AA were low in subjects with hypertension, diabetes mellitus and CHD.85 South Asian Indians, who are at high risk of developing metabolic syndrome X, have significantly lower concentrations of AA, EPA, and DHA compared to healthy Canadians and Americans.96 Thus, PUFAs and cytokines interact with each other and play a significant role in metabolic syndrome X.

Neurological conditions: schizophrenia, Huntington’s disease, Alzheimer’s disease

Low-grade inflammation plays a role in schizophrenia, Huntington’s disease and Alzheimer’s disease. Patients with schizophrenia have increased concentrations of pro-inflammatory cytokines both in the systemic circulation and cerebrospinal fluid, and showed decreased EPA and DHA in the plasma phospholipid. Clinical trials showed that supplementation of ethyl EPA is of significant benefit to these patients.97

A diet high in DHA slowed the progression of Alzheimer’s disease both in experimental animals and humans. DHA enabled mice to perform better on memory tests. These studies suggest that people who are genetically or otherwise predisposed to the disease may be able to delay it by increasing their DHA intake.99,100

Huntington’s disease is an inherited neurodegenerative disorder due to a mutation in exon 1 of the Huntingtin gene that encodes a stretch of polyglutamine (poly Q) residues close to the N-terminus of the Huntingtin protein. Aggregated poly Q residues are toxic to the neuronal cells. Transgenic R6/1 mice that develop motor abnormalities of Huntington’s disease showed increased survival rates and decreased neurologic deficits when were supplemented with ethyl EPA,99 suggesting that unsaturated fatty acids may prevent or arrest poly Q aggregation. These results suggest that PUFAs are useful in various neurological diseases. Understanding the molecular mechanisms of action of EPA/DHA as to why DHA is useful in Alzheimer’s disease whereas ethyl EPA is of benefit in Huntington’s disease and schizophrenia may throw more light in the pathobiology of these diseases.

Perinatal origins of adult diseases and its relationship with EFAs/PUFAs

Mice overexpressing 11b-hydroxysteroid dehydrogenase type 1 (11b-HSD-1) enzyme selectively in adipose tissue develop abdominal obesity, exhibit insulin resistance, type 2 diabetes, hyperlipidemia, hyperphagia, and hyperleptinemia (reviewed in 91), features that are similar to those seen in metabolic syndrome X. This suggests that abdominal obesity is akin to localized Cushing’s syndrome. Increased activity of 11b-HSD-1 in the abdominal adipose tissue leads to enhanced formation of corticosterone locally compared to subcutaneous adipose tissue, which could be one reason for the development of abdominal obesity.

There is reasonable evidence to suggest that cardiovascular disease and type 2 diabetes may have its origins early in life.95 For instance, low birth weight leads to high prevalence of metabolic syndrome X in later life. However, it was also proposed that postnatal nutrition

www.japi.org © JAPI • VOL. 54 • APRIL 2006
and growth are equally important in the development of metabolic syndrome X in later life. If so, it is expected that improved obstetric care, general increase in the standard of living, and better nutrition during pregnancy should have led to a decrease in the incidence of metabolic syndrome X. Instead, the incidence of obesity, type 2 diabetes, hypertension, and CHD has increased. This implies that low birth weight could no longer account for the rapidly increasing incidence of metabolic syndrome X.

Previously, I proposed that high-energy food, saturated (including cholesterol) and trans-fats enhance TNF-α, IL-6 and CRP and decrease the synthesis, secretion, and action of IL-4 and IL-10. This, in turn, augments the activity of 11b-HSD-1 that causes insulin resistance, IGT, abdominal obesity and development of metabolic syndrome X.91

Both ω-3 and ω-6 fatty acids are essential for fetal growth and development including brain16, 20. Newborn infants, especially pre-term infants, have limited capacity to form EPA, DHA and AA. EPA and DHA increase birth weight by prolonging gestation and/or by increasing the fetal growth rate, whereas AA status correlated with growth during the first year of life. Furthermore, PUFAs increase brain acetylcholine levels and thus, augment parasympathetic activity that leads to an increase in heart rate variability, a property that explains the ability of these fatty acids to suppress cardiac arrhythmias and prevent sudden cardiac death.91 Acetylcholine is also known to have anti-inflammatory action by suppressing the production of TNF-α. These evidences suggest that PUFAs not only function as endogenous statins, β-blockers, PPAR agonists, ACE inhibitors, anti-inflammatory, anti-hypertensive, and antibiotic-like molecules and but also enhance adiponectin levels and decrease insulin resistance,91 which explains the beneficial action of PUFAs against CHD, atherosclerosis, and hypertension.

Malnutrition can be both under nutrition and over nutrition. Maternal protein restriction or increased consumption of saturated and/or trans-fatty acids and energy rich diets (maternal over nutrition) during pregnancy decrease the activity of D6 and D5 desaturases that are essential for the metabolism of dietary EFAs. Perinatal protein depletion leads to almost complete absence of activities of D6 and D5 desaturases in fetal liver and placenta (reviewed in 91). Thus, both protein deficiency and high-energy diet decreases the activities of D6 and D5 desaturases. Hence, maternal malnutrition leads to maternal and fetal deficiency of EPA, DHA and AA.

EPA, DHA, and AA inhibit TNF-α and IL-6 synthesis. Hence, EPA, DHA and AA deficiency that occurs due to maternal malnutrition increases the generation of TNF-α and IL-6. This, in turn, causes insulin resistance. This indicates that maternal and fetal sub-clinical deficiency of EPA, DHA and AA increases TNF-α and IL-6 in the fetus. Prenatal exposure to TNF-α produces obesity, and obese subjects have high levels of TNF-α and IL-6. Low plasma and tissue concentrations of EPA, DHA, and AA decrease adiponectin levels that further aggravate insulin resistance. TNF-α and IL-6 increase the activity of 11b-HSD-1 that causes abdominal obesity, a characteristic feature of metabolic syndrome X. These evidences imply that metabolic syndrome X is due to perinatal deficiency of EPA, DHA and AA.91

Conclusions and future directions

It is evident from the preceding discussion that EFAs and their metabolites such as GLA, AA, EPA, DHA, eicosanoids, LXs, resolvins, and NPD1 have many actions and participate in several diseases processes (Fig. 2). In this context, it is important to note that certain PUFAs such as GLA have both anti-mutagenic and anti-cancer actions that have been discussed in detail elsewhere.56 Studies revealed that mutagens and carcinogens block Δ6 and Δ5 desaturases in normal cells much before their conversion into malignant cells. Pre-treatment or simultaneous treatment with GLA completely prevented DNA damage induced by mutagens and carcinogens,56 implying that GLA and other PUFAs could function as endogenous anti-mutagenic and anti-cancer molecules. GLA has selective tumoricidal action and is effective against human malignant glioma and other cancers.56

It is interesting to note that NO can react with PUFAs to yield their respective nitroalkene derivatives that can be detected in plasma. These nitroalkene derivatives of various EFAs induce vascular relaxation, inhibit neutrophil degranulation and superoxide formation, inhibit platelet activation, and have endogenous PPAR-γ ligand activity and decay in the blood to release NO. This suggests that EFAs/PUFAs not only form precursors to various eicosanoids, resolvins, LXs, and NPD1 but also react with various other molecules to form novel compounds that have significant biological activity.

The major question is how these simple fatty acids are able to have so many biological and at times diametrically opposite actions. One reason could be their ability to give rise to many metabolites that have specific biological actions. Furthermore, these fatty acids when incorporated into the cell membrane alter its properties including fluidity that, in turn, modulates the number and affinity of various receptors to their respective growth factors, hormones, peptides and proteins. Yet another action is their ability to form complexes with other biologically active molecules as is seen with NO to form various nitroalkene derivatives. Formation of such complexes between EFAs and other biologically active molecules could impart specific and distinctive
properties to these newly formed entities that in turn may show varied biological actions. Deciphering the formation of such complexes is not only interesting but also challenging since such complexes may form the basis of understanding certain less well understood physiological and pathological processes.

Although structurally EFAs are simple, they form precursors to a variety of compounds with many biological actions. We are yet to understand the molecular triggers that facilitate the formation of specific biologically active molecules in various cells and tissues. Once this is known, it will be possible to selectively enhance the formation of the desired lipid to obtain a specific function or action. Chemical synthesis of stable and potent eicosanoids, LXs, resolvins, and NPD1 would help in the management of several inflammatory conditions. In view of their varied actions, EFAs/PUFAs and their products may form basis for the development of many nutraceuticals and drugs.

REFERENCES


Das UN. A defect in the activity of Δ⁵ and Δ⁶ desaturases may be a predisposing factor to the development of insulin resistance syndrome. Prostaglandins Leukotrienes Essen Fatty Acids 2005;72:343-50.


Das UN. Do unsaturated fatty acids function as endogenous anti-bacterial and anti-viral molecules? Am J Clin Nutr, in press.


Das UN. A defect in the activity of Δ⁵ and Δ⁶ desaturases may be a predisposing factor to the development of insulin resistance syndrome. Prostaglandins Leukotrienes Essen Fatty Acids 2005;72:343-50.


Das UN. Do unsaturated fatty acids function as endogenous anti-bacterial and anti-viral molecules? Am J Clin Nutr, in press.


Das UN. A defect in the activity of Δ⁵ and Δ⁶ desaturases may be a predisposing factor to the development of insulin resistance syndrome. Prostaglandins Leukotrienes Essen Fatty Acids 2005;72:343-50.


Das UN. Do unsaturated fatty acids function as endogenous anti-bacterial and anti-viral molecules? Am J Clin Nutr, in press.


Das UN. A defect in the activity of Δ⁵ and Δ⁶ desaturases may be a predisposing factor to the development of insulin resistance syndrome. Prostaglandins Leukotrienes Essen Fatty Acids 2005;72:343-50.


Das UN. Do unsaturated fatty acids function as endogenous anti-bacterial and anti-viral molecules? Am J Clin Nutr, in press.


Das UN. A defect in the activity of Δ⁵ and Δ⁶ desaturases may be a predisposing factor to the development of insulin resistance syndrome. Prostaglandins Leukotrienes Essen Fatty Acids 2005;72:343-50.


Das UN. Do unsaturated fatty acids function as endogenous anti-bacterial and anti-viral molecules? Am J Clin Nutr, in press.


---

**Announcement**

**Third Madras Diabetes Research Foundation (MDRF) – American Diabetes Association (ADA) Postgraduate Course on Diabetes, at Chennai, India, 6 - 8th October 2006.**

The Third MDRF-ADA Postgraduate Course on Diabetes will be held from 6th to 8th October 2006 at Chennai, India. The meeting will be hosted by the Madras Diabetes Research Foundation, Chennai.

For further details, contact: Dr. V Mohan, M.D., FRCP, Ph.D., D.Sc., FNASc (or) Dr. Rema Mohan, MBBS, D.O., Ph.D., Madras Diabetes Research Foundation and Dr. Mohan’s Diabetes Specialities Centre, No. 4 Conran Smith Road, Gopalapuram, Chennai 600 086, India.

Phone : (91 44) 28359048, 28359051, 28353351; Fax : (91 44) 28350935; E-mail: mvdsc@vsnl.com

Also visit our website at [www.mdrf-ada.com](http://www.mdrf-ada.com) or [www.drmohansdiabetes.com](http://www.drmohansdiabetes.com) for details regarding registration etc.