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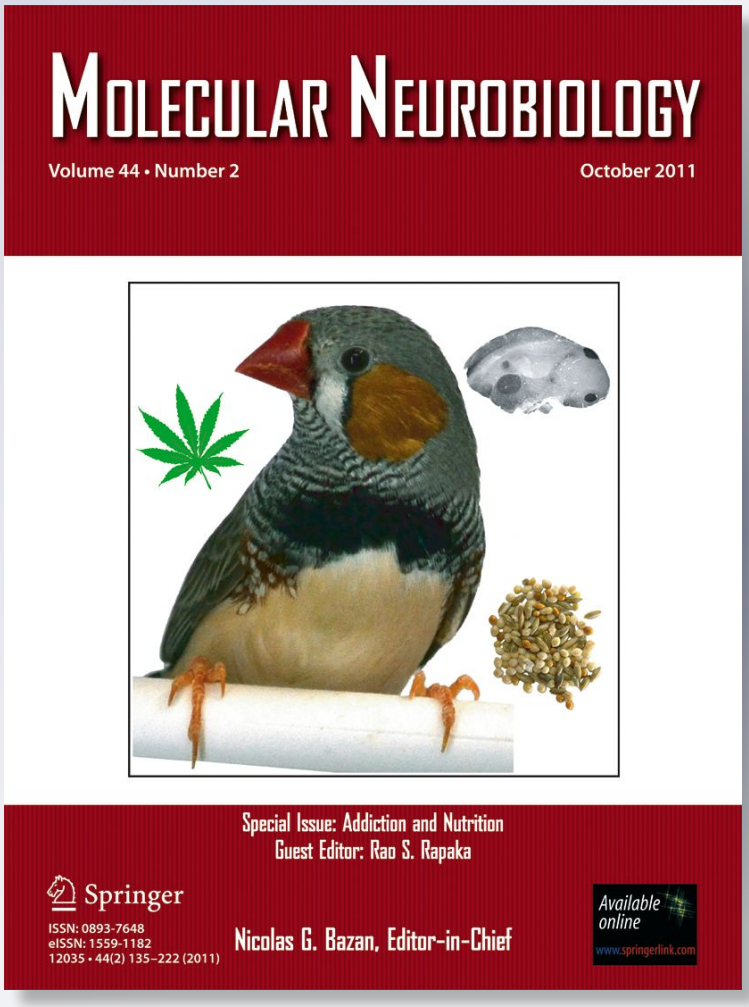

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Evolutionary Aspects of Diet: The Omega-6/Omega-3 Ratio and the Brain

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Abstract Several sources of information suggest that human beings evolved on a diet that had a ratio of omega-6 to omega-3 fatty acids (FA) of about 1/1; whereas today, Western diets have a ratio of 10/1 to 20–25/1, indicating that Western diets are deficient in omega-3 FA compared with the diet on which humans evolved and their genetic patterns were established. Omega-6 and omega-3 FA are not interconvertible in the human body and are important components of practically all cell membranes. Studies with nonhuman primates and human newborns indicate that docosahexaenoic acid (DHA) is essential for the normal functional development of the brain and retina, particularly in premature infants. DHA accounts for 40% of the membrane phospholipid FA in the brain. Both eicosapentaenoic acid (EPA) and DHA have an effect on membrane receptor function and even neurotransmitter generation and metabolism. There is growing evidence that EPA and DHA could play a role in hostility and violence in addition to the beneficial effects in substance abuse disorders and alcoholism. The balance of omega-6 and omega-3 FA is important for homeostasis and normal development throughout the life cycle.

Keywords Omega-6 and omega-3 fatty acid balance · Brain development · Neurotransmitters · Metabolism · Aggression · Violent behavior · Drug abuse · Genetics polymorphism

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Introduction

The interaction of genetics and environment, nature, and nurture is the foundation for all health and disease. In the last two decades, using the techniques of molecular biology and genetics, it has been shown that genetic factors determine susceptibility to disease and environmental factors determine which genetically susceptible individuals will be affected [1–6]. Nutrition is an environmental factor of major importance. Using the tools of molecular biology and genetics, research is defining the mechanisms by which genes influence nutrient absorption, metabolism and excretion, taste perception, and degree of satiation; and the mechanisms by which nutrients influence gene expression. Whereas major changes have taken place in our diet over the past 10,000 years since the beginning of the Agricultural Revolution, our genes have not changed. The spontaneous mutation rate for nuclear DNA is estimated at 0.5% per million years. Therefore, over the past 10,000 years there has been time for very little change in our genes, perhaps 0.005%. In fact, our genes today are very similar to the genes of our ancestors during the Paleolithic period 40,000 years ago, at which time our genetic profile was established [7]. Genetically speaking, humans today live in a nutritional environment that differs from that for which our genetic constitution was selected. Studies on the evolutionary aspects of diet indicate that major changes have taken place in our diet, particularly in the type and amount of essential fatty acids and in the antioxidant content of foods [7–11] (Fig. 1).

Today industrialized societies are characterized by (1) an increase in energy intake and decrease in energy expenditure; (2) an increase in saturated fat, omega-6 fatty acids, and *trans*-fatty acids, and a decrease in omega-3 fatty acid intake; (3) a decrease in complex carbohydrates and fiber

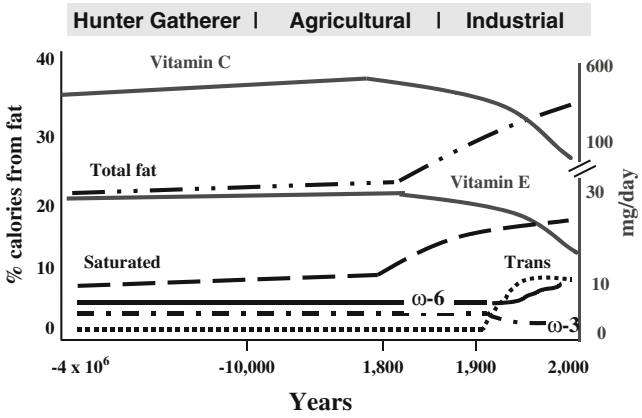

Fig. 1 Hypothetical scheme of fat, fatty acid (ω6, ω3, *trans*, and total) intake (as percent of calories from fat) and intake of vitamins E and C (milligrams per day). Data were extrapolated from cross-sectional analyses of contemporary hunter–gatherer populations and from longitudinal observations and their putative changes during the preceding 100 years [9]

intake; (4) an increase in cereal grains and a decrease in fruits and vegetables intake; and (5) a decrease in protein, antioxidants, vitamin D, and calcium intake [7, 9, 12–15]. The increase in *trans*-fatty acids is detrimental to health [16]. In addition, *trans*-fatty acids interfere with the desaturation and elongation of both omega-6 and omega-3 fatty acids, thus further decreasing the amount of arachidonic acid, eicosapentaenoic acid, and docosahexaenoic acid availability for human metabolism [17].

The beneficial health effects of omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) were described first in the Greenland Eskimos who consumed a high seafood diet and had low rates of coronary heart disease, asthma, type 1 diabetes mellitus, and multiple sclerosis. Since that observation, the beneficial health effects of omega-3 fatty acids have been extended to include benefits related to cancer, inflammatory bowel disease, rheumatoid arthritis, psoriasis, and mental health [18] (Table 1).

Imbalance of Omega-6/Omega-3

Food technology and agribusiness provided the economic stimulus that dominated the changes in the food supply [19, 20]. From per capita quantities of foods available for consumption in the US national food supply in 1985, the amount of EPA is reported to be about 50 mg per capita/day and the amount of DHA is 80 mg per capita/day. The two main sources are fish and poultry [21]. It has been estimated that the present Western diet is "deficient" in omega-3 fatty acids with a ratio of omega-6 to omega-3 of 15–20/1, instead of 1/1 as is the case with wild animals and presumably human beings [7–11, 13, 22–24] (Table 2).

Before the 1940s cod-liver oil was ingested mainly by children as a source of vitamin A and vitamin D with the usual dose being a teaspoon. Once these vitamins were synthesized, consumption of cod-liver oil was drastically decreased, contributing further to the decrease of EPA and DHA intake. Table 3 shows ethnic differences in fatty acid concentrations in thrombocyte phospholipids, the ratios of omega-6/omega-3 fatty acids, and percentage of all deaths from cardiovascular disease [25].

An absolute and relative change of omega-6/omega-3 in the food supply of Western societies has occurred over the last 150 years. A balance existed between omega-6 and omega-3 for millions of years during the long evolutionary history of the genus Homo, and genetic changes occurred partly in response to these dietary influences. During evolution, omega-3 fatty acids were found in all foods consumed: meat, wild plants, eggs, fish, nuts, and berries [26–35]. Studies by Cordain et al. [36] on wild animals confirm the original observations of Crawford and Sinclair et al. [23, 37]. However, rapid dietary changes over short periods of time as have occurred over the past 100–150 years is a totally new phenomenon in human evolution [13, 15, 38–40] (Table 4).

Biological Effects and the Omega-6/Omega-3 Ratio

About 80 years ago (1929–1930) Burr and Burr were the first to discover the importance of linoleic acid (LA) 18:2ω-6 and alpha-linolenic acid (ALA) 18:3ω-3 in restoring the effects caused by the fat-free diet in deprived animals. They coined the term "essential fatty acids" (EFAs). Whereas healthy skin and successful growth, reproduction and lactation were obtained in mammals fed LA as the only source of EFA, linolenic acid was found to permit growth but was unable to prevent the skin lesions of EFA deficiency or support reproduction [41].

Today we know that LA and ALA are essential for normal growth and development of human beings. The two families of omega-6 (LA) and omega-3 (ALA) fatty acids are physiologically and metabolically distinct, cannot be synthesized in the human body and must be obtained from the diet. Figure 2 shows the metabolism of LA and ALA into very long chain polyunsaturated fatty acids (LC-PUFAs) through a series of desaturases and elongases. Both LA and ALA use the same enzymes and compete with each other for enzyme availability. During evolution, there was a balance in the intake of LA and ALA with a ratio of ω-6/ω-3=1; whereas, today in Western societies the ratio is about 16/1 ω-6/ω-3 due to the high intake of vegetable oils-soybean, corn oil, sunflower, safflower, and linseed oil, which are high in 18:2ω-6 [2]. LA is found in high

Table 1 Effects of n-3 fatty acids on factors involved in the pathophysiology of atherosclerosis, inflammation, and aging

Factor	Function	Effect of n-3 fatty acid
Arachidonic acid	Eicosanoid precursor, aggregates platelets, and stimulates white blood cells	↓
Thromboxane A_2	Platelet aggregation, vasoconstriction, and increase of intracellular Ca^{++}	↓
$PGI_{2/3}$	Prevent platelet aggregation, vasodilation, and increase cAMP	↑
LTB_4	Neutrophil chemoattractant and increase of intracellular Ca^{++}	↓
Fibrinogen	A member of the acute-phase response and a blood clotting factor	↓
Tissue plasminogen activator	Increase endogenous fibrinolysis	↑
PAF	Activates platelets and white blood cells	↓
PDGF	Chemoattractant and mitogen for smooth muscles and macrophages	↓
Oxygen free radicals	Cellular damage, enhance LDL uptake via scavenger pathway, and stimulate arachidonic acid metabolism	↓
Lipid hydroperoxides	Stimulate eicosanoid formation	↓
Interleukin 1 and tumor necrosis factor	Stimulate neutrophil O_2 free radical formation, stimulate lymphocyte proliferation, stimulate PAF, express intercellular adhesion molecule-1 on endothelial cells, and inhibit plasminogen activator, thus, procoagulants	↓
Interleukin-6	Stimulates the synthesis of all acute-phase proteins involved in the inflammatory response: C-reative protein, serum amyloid A, fibrinogen, α_1-chymotrypsin, and haptoglobin	↓
CRP	An acute-phase reactant and an independent risk factor for cardiovascular disease	↓
Endothelial-derived relaxation factor	Reduces arterial vasoconstrictor response	↑
Insulin sensitivity		↑
VLDL		↓
HDL	Decreases the risk for coronary heart disease	↑
Lp(a)	Lipoprotein(a) is a genetically determined protein that has atherogenic and thrombogenic properties	↓
Triglycerides and chylomicrons	Contribute to postprandial lipemia	↓
Telomeres	Have anti-aging effects whereas LA promotes shortening of telomeres and aging	↑
Resolvin E_1–E_2 (EPA)	Anti-inflammatory important in the resolution of inflammation	↑
Resolvin D_1–D_2 (DHA)	Anti-inflammatory important in the resolution of inflammation	↑
Neuroprotectin (DHA)	Protects brain and is important in the patients with strokes or trauma	↑
PPAR	Upregulates the expression of genes involved in lipid metabolism and downregulates the expression of genes involved in inflammation and suppresses NFκB	↑

PGI2/3 prostacyclin, *LTB4* leukotriene, *PAF* platelet-activating factor, *PDGF* platelet-derived growth factor, *CRP* C-reactive protein, *EPA* eicosapentaenoic acid, *DHA* docosahexaenoic acid

amounts in grains with the exception of flaxseed, chia, perilla, rapeseed, and walnuts that are rich in ALA. The green leaves of plants, particularly wild plants are higher in ALA than LA [8, 26, 42, 43].

Table 2 Ratios of dietary omega-6/omega-3 fatty acids in the late paleolithic period and in current western diets (USA; g/day)

	Paleolithic	Western
LA:ALA	0.70	18.75
AA+DTA/EPA+DPA+DHA	1.79	3.33
Total	0.79	16.74

Reprinted with permission from reference [15]

LA Linoleic acid, *ALA* Linolenic acid, *AA* Arachidonic acid, *EPA* Eicosapentaenoic acid, *DTA* docosatetranoic acid, *DPA* docosapentaenoic acid, *DHA* docosahexaenoic acid

The capacity for desaturation and chain elongation of polyunsaturated fatty acids (PUFAs) appears to be limited and variable. From isotope-labeled ALA feeding studies, the range of conversion of ALA to EPA has been estimated between 0.2% and 21% [44]. The PUFA composition of phospholipids has been shown to be associated with normal growth and development, as well as in the outcome of chronic diseases such as coronary heart disease (CHD), hypertension, cancer, arthritis, mental health, allergies and other autoimmune diseases, since both omega-6 and omega-3 PUFAs are processed to powerful promoters of eicosanoids such as prostaglandins and leukotrienes (Fig. 3). Plasma levels of LC-PUFAs are determined by both dietary intake and endogenous metabolism. Desaturases and elongases catalyze the conversion of PUFAs in humans. Figure 2 shows the metabolic pathway of omega-6

Table 3 Ethnic differences in fatty acid concentrations in thrombocyte phospholipids and percentage of all deaths from cardiovascular disease

Data modified from reference [25]

	Europe and USA (%)	Japan (%)	Greenland Eskimos (%)
Arachidonic acid (20:4ω6)	26	21	8.3
Eicosapentaenoic acid (20:5ω3)	0.5	1.6	8.0
Ratio of ω6/ω3	50	12	1
Mortality from cardiovascular disease	45	12	7

and omega-3 fatty acids. The key enzymes in this pathway are the delta-5 and delta-6 desaturases, which are encoded by fatty acid desaturase (FADS)1 and FADS2, respectively [45, 46]. They are the rate limiting enzymes in the synthesis of LC-PUFA, arachidonic acid (AA), EPA, and DHA from their dietary precursors LA and ALA. AA and EPA are the parent fatty acids for the formation of eicosanoids and DHA for docosanoids.

Competition between the omega-6 and omega-3 fatty acids occurs in prostaglandin formation. EPA competes with AA for prostaglandin and leukotriene synthesis at the cyclooxygenase and lipoxygenase level (Fig. 3). When humans ingest fish or fish oil, the EPA and DHA from fish or fish oil lead to: (1) a decreased production of prostaglandin E_2 (PGE_2) metabolites; (2) a decrease in thromboxane A_2, a potent platelet aggregator and vasoconstrictor; (3) a decrease in leukotriene B_4 formation, an inducer of inflammation and a powerful inducer of leukocyte chemotaxis and adherence; (4) an increase in thromboxane A_3, a weak platelet aggregator and a weak vasoconstrictor; (5) an increase in prostacyclin PGI_3, leading to an overall increase in total prostacyclin by increasing PGI_3 without a decrease in PGI_2. Both PGI_2 and PGI_3 are active vasodilators and inhibitors of platelet aggregation; and (6) an increase in leukotriene B_5, a weak inducer of inflammation and a weak chemotactic agent [47, 48]. Omega-3 fatty acids modulate prostaglandin metabolism and decrease triglycerides; and in high doses lower cholesterol and have antithrombotic and anti-inflammatory properties. These studies have been extensively reviewed [49–54]. In the early phase of inflammation, excessive amounts of interleukins and lipid mediators are released and play a crucial role. Pro-inflammatory eicosanoids of AA metabolism are released from membrane phospholipids in the course of inflammatory activation. EPA is released to compete with AA for enzymatic metabolism inducing the production of less inflammatory and chemotactic derivatives.

AA is involved in growth and produces PGE_2, which is important for the normal development of many organs and cells including the central nervous system [55–60]. DHA is found in high amounts in the membranes of brain and retina and is critical for proper neurogenesis, neurotransmitter metabolism, neuroprotection and vision. The consumption of high amounts of DHA has been associated with multiple health benefits including brain and retinal development, aging, memory formation, synaptic membrane function, photoreceptor biogenesis and function, and neuroprotection. DHA is essential for pre-natal brain development [61, 62].

The FADS1 and FADS2 gene cluster involved in the metabolic pathway of LA and ALA as well as the enzymes involved in the production of eicosanoids, 5-lipoxygenase (5-LO), and cyclooxygenase from the AA and EPA, are polymorphic. Recent studies on their polymorphisms indicate that the minor alleles of the genetic variants in FADS1 and FADS2 are associated with higher LA and lower AA levels in red blood cell membrane and plasma phospholipids which may influence the estimation of

Table 4 Omega-6/omega-3 ratios in various populations

Population	ω6/ω3
Paleolithic	0.79
Greece prior to 1960	1.00–2.00
Current Japan	4.00
Current India, rural	5–6.1
Current UK and northern Europe	15.00
Current USA	16.74
Current India, urban	38–50

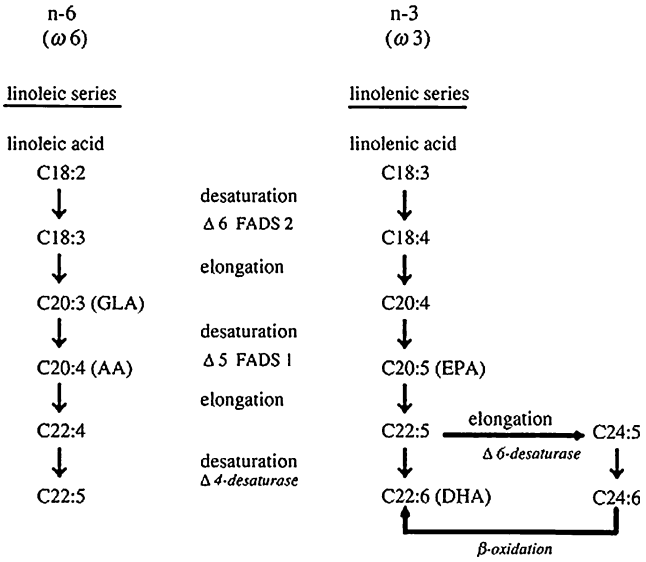

Fig. 2 Desaturation and elongation of v-3 and v-6 fatty acids. The enzymes D6 and D5 desaturases are encoded by FADS2 and FADS1, respectively

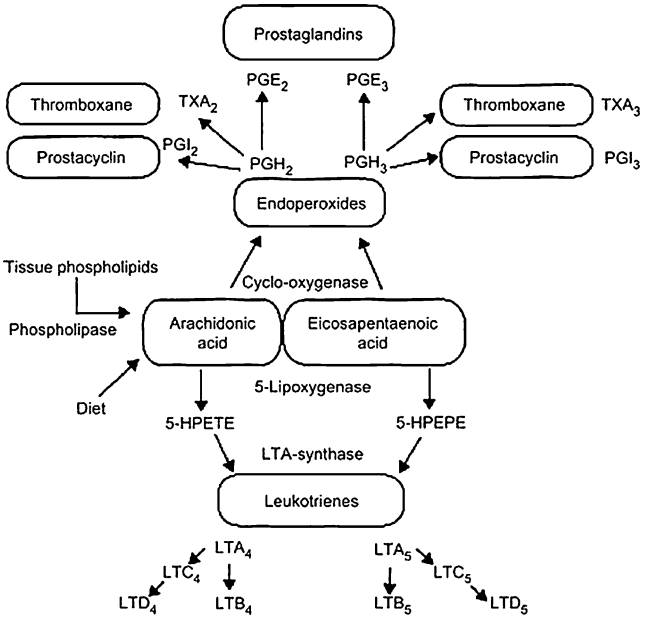

Fig. 3 Oxidative metabolism of arachidonic acid and eicosapentaenoic acid by the cyclooxygenase and 5-lipoxygenase pathways. *5-HPETE* 5-hydroperoxyeicosatetranoic acid, *5-HPEPE* 5-hydroxyeicosapentaenoic acid

dietary requirements [63, 64], particularly during pregnancy and lactation [65] as well as the infant's IQ [66]; whereas, an increase in the activity of the desaturase increases the AA-to-LA ratio and the risk for CHD [67]. Furthermore, genetic variants in the 5-LO and cyclooxygenase-2 genes have been associated with increased risk for CHD [68] and cancer [69], respectively.

Omega-3 Fatty Acids and Newly Identified Lipid Mediators: Lipoxins, Resolvins, and Protectins

Recent studies have shown that additional lipid mediators are produced from AA, EPA, and DHA with potent anti-inflammatory properties [62]. Lipoxins are derived from AA as a result of cell-cell interaction and the sequential transformation by different lipoxygenases. Leucocyte 5-lipoxygenase generates LT4 from AA which is then transformed to the lipoxin LXA4 in platelets by the oxidase activity of their 12-lipoxygenase. In addition to their anti-inflammatory properties lipoxins have potent pro-resolution properties, inhibit the formation of inflammatory cytokines, immune cell proliferation and migration. In the presence of aspirin, the acetylation of cyclo-oxygenase 2 enables it to act as a lipoxygenase forming the lipoxin precursor 15-hydroxy eicosatetraenoic acid from AA, which is then transformed by leucocyte 5-lipoxygenase to 15-epi-LXA4 or 15-epi LXB4 referred to as aspirin-triggered lipoxins. These aspirin-triggered lipoxins seem to be more potent anti-inflammatory agents than the conventional LX4 [70].

In analogy to the aspirin-triggered lipoxins from AA, bioactive mediators are also produced from EPA+DHA. Serhan and his group [62] used lipidomics and informatics in studies on EPA and DHA metabolites in the resolution of inflammation which are called resolvins. The resolvin from EPA is RvE1. RvE1 inhibits nuclear factor-κB by tumor necrosis factor-α (TNF-α). ChemR23 is the receptor for RvE1 and it is a specific G-protein-coupled receptor. Transcription of ChemR23 is found in cardiovascular, gastrointestinal, renal, brain, and myeloid tissue. The ChemR23 shares homology with the receptor identified for the AA derived aspirin-triggered lipoxins but is molecularly distinct.

Resolvins are derived from EPA and DHA with two chemically unique structural forms, the E-series and the D-series, respectively. Resolvin E_1 is produced in healthy individuals and is increased in the plasma of individuals taking aspirin and or EPA. DHA is the substrate for two groups of resolvins produced by different biosynthetic routes, referred to as the 17S and 17RD-series resolvins during the resolution of inflammatory exudates. D-series resolvins have potent anti-inflammatory actions and are particularly interesting because the brain, synapses, and retina are highly enriched in DHA. The D-series resolvins are of interest in the control of resolution of inflammation in host defense and in neural tissues.

Another class of lipid mediators produced from DHA are the 10–17S-docosatriene, now known as protectins. When produced by nervous tissues this protectin is termed neuroprotectin D_1 because of its unique biosynthetic origin from free DHA in the brain [61]. Sterospecific oxygenated derivatives of DHA created through lipoxygenase action on free DHA further generate neuroprotectin D_1 that elicits potent cyto- and neuroprotective effects. NPD1 is important in homeostatic brain function (see chapter by Bazan et al. in this volume). Protectin D_1 blocks T cell migration in vivo, reduces TNF and Interferon-γ secretion and promotes T cell apoptosis [61]. Resolvin E_1 and protectin D_1 derived from EPA+DHA, respectively, are potent resolution agonists that activate cell type, neutrophils, macrophages, and epithelial cells to accelerate resolution. Lipoxins, resolvins, and protectins have potent multilevel mechanisms of action in disease models and promote resolution in animal models of oral, lung, ocular, kidney, skin and gastrointestinal inflammation, as well as in ischemia-reperfusion injury and angiogenesis. Lipoxins, resolvin E_1, and protectins act on T cells, dendritic cells, and phagocytic cells; therefore they represent a link between the innate and the immune system. Considering that lipoxins, resolvin E_1, and protectins are produced from AA, EPA+DHA, it follows that these fatty acids represent a molecular link between the two systems.

Inflammation is at the base of many chronic diseases such as cardiovascular disease, obesity, diabetes, arthritis,

mental illnesses and cancer, as well as many autoimmune diseases. These diseases are characterized by increased amounts of IL-1 and IL-6. Increased dietary intake of omega-6 fatty acids is associated with higher levels of TXA2, and LTB4. Leuoktriene B4 is a proinflammatory AA metabolite that along with IL-1 and IL-6 contributes to inflammation. The discovery of the newly identified mediators lipoxins, resolvins, protectins, and neuroprotectins form AA (lipoxins), EPA (resolvins), and DHA (protectins and neuroprotectins) indicate that the resolution of inflammation is not just a passive termination of inflammation, but rather an active biochemical and metabolic process. These families of endogenous pro-resolution molecules are not immunosuppressive but instead function in the resolution of inflammation by activating specific mechanisms to promote homeostasis [70].

The Balance of Omega-6/Omega-3 Fatty Acids Is Important for Health: The Evidence from Gene Transfer Studies

Further support for the need to balance the omega-6/omega-3 EFA comes from the studies of Kang et al. [71] and Ge et al. [72], which clearly show the ability of both normal rat cardiomyocytes and human breast cancer cells in culture to form all the omega-3's from omega-6 fatty acids when fed the cDNA encoding omega-3 fatty acid desaturase obtained from the roundworm *Caenorhabditis elegans*. The omega-3 desaturase efficiently and quickly converted the omega-6 fatty acids that were fed to the cardiomyocytes in culture to the corresponding omega-3 fatty acids. Thus, omega-6 LA was converted to omega-3 ALA and AA was converted to EPA, so that at equilibrium, the ratio of omega-6 to omega-3 PUFA was close to 1/1. Further studies demonstrated that the cancer cells expressing the omega-3 desaturase underwent apoptotic death whereas the control cancer cells with a high omega-6/omega-3 ratio continued to proliferate [73]. More recently, Kang et al. [74, 75] and Lai et al. [76] showed that transgenic mice and pigs expressing the *C. elegans fat-1* gene encoding an omega-3 fatty acid desaturase are capable of producing omega-3 from omega-6 fatty acids, leading to enrichment of omega-3 fatty acids with reduced levels of omega-6 fatty acids in almost all organs and tissues, including muscles and milk, with no need of dietary omega-3 fatty acid supply. This discovery provides a unique tool and new opportunities for omega-3 research, and raises the potential of production of *fat-1* transgenic livestock as a new and ideal source of omega-3 fatty acids to meet the human nutritional needs. Furthermore, the transgenic mouse model is being used widely by scientists for the study of chronic diseases and for the study of mechanisms of the beneficial effects of omega-3 fatty acids in decreasing the risk of various forms of cancer and CHD [77]. The fat-1 transgenic mice produce and store higher levels of EPA+DHA in their tissues than wild type mice, and as a result generate increased levels of resolvins and protectins.

Omega-3 Fatty Acids and Gene Expression

Previous studies have shown that fatty acids released from membrane phospholipids by cellular phospholipases, or made available to the cell from the diet or other aspects of the extracellular environment, are important cell signaling molecules. They can act as second messengers or substitute for the classical second messengers of the inositide phospholipid and the cyclic AMP signal transduction pathways. They can also act as modulator molecules mediating responses of the cell to extracellular signals. Recently it has been shown that fatty acids rapidly and directly alter the transcription of specific genes [78]. In the case of genes involved in inflammation, such as IL-1β, EPA and DHA suppress IL-1β mRNA whereas AA does not, and the same effect appears in studies on growth-related early response gene expression and growth factor [78]. In the case of vascular cell adhesion molecule (VCAM), AA has a modest suppressing effect relative to DHA. The latter situation may explain the protective effect of fish oil toward colonic carcinogenesis, since EPA and DHA did not stimulate protein kinase C. PUFA regulation of gene expression extends beyond the liver and includes genes such as adipocyte glucose transporter-4, lymphocyte stearoyl-CoA desaturase-2 in the brain, peripheral monocytes (IL-1β and VCAM-1), and platelets (platelet-derived growth factor). Whereas some of the transcriptional effects of PUFA (both omega-6 and omega-3 fatty acids) appear to be mediated by eicosanoids, the PUFA suppression of lipogenic and glycolytic genes is independent of eicosanoid synthesis, and appears to involve a nuclear mechanism directly modified by PUFA.

Omega-3 Fatty Acids in Mental Health

Psychologic stress in humans induces the production of proinflammatory cytokines such as IFNγ, TNFα, IL-6, and IL-1. An imbalance of omega-6 and omega-3 PUFA in the peripheral blood causes an overproduction of proinflammatory cytokines. There is evidence that changes in fatty acid composition are involved in the pathophysiology of major depression [79]. Changes in serotonin (5-HT) receptor number and function caused by changes in PUFA provide the theoretical rationale connecting fatty acids with the current receptor and neurotransmitter theories of depression

[80–84]. The increased C20/4ω6/C20/5ω3 ratio and the imbalance in the omega-6/omega-3 PUFA ratio in major depression may be related to the increased production of proinflammatory cytokines and eicosanoids in that illness [82]. There are a number of studies evaluating the therapeutic effect of EPA and DHA in major depression. Stoll and colleagues [85, 86] have shown that EPA and DHA prolong remission, that is, reduce the risk of relapse in patients with bipolar disorder.

Kiecolt-Glaser et al. studied depressive symptoms, omega-6/omega-3 fatty acid ratio and inflammation in older adults [87]. As the dietary ratio of omega-6/omega-3 increased, the depressive symptoms, TNF-α, IL-6, and IL-6 soluble receptor increased. The authors concluded that diets with a high omega-6/omega-3 ratio may enhance the risk for both depression and inflammatory diseases.

Conklin et al. [88] studied postmortem changes in brain fatty acids within the anterior cingulate cortex according to the presence of depression at the time of death. A significant negative correlation between age and the ratio of AA/DHA was found in patients but not in controls. The decreases in DHA may be caused, in part, by the diminished formation of EPA (20:5w3) which is derived from 20:4w-3 through a delta-5 desaturase reaction. An increased AA/DHA ratio could be considered a biomarker for depression that results from higher dietary intake of AA or endogenous decrease production of DHA.

While essential fatty acid deficiencies may be due to dietary intake, a number of enzymatic desaturation and elongation processes are required for longer chain fatty acids to be metabolized from the shorter chain parent precursor fatty acids (Fig. 2). Therefore individuals vulnerable for the development of affective disorders, because of genetic variation in desaturation and elongation of omega-6 and omega-3 metabolic pathways may not achieve an optimal level of serum or brain fatty acids. In fact increased free radical production, secondary to behavioral factors associated with mood disorders such as smoking, alcohol consumption, poor sleep quality and lack of exercise, could reduce the availability of PUFA despite adequate dietary patterns and intake. Furthermore, an inability to optimally transfer the AA, EPA and DHA across the blood brain barrier could lead to reduced concentration of brain fatty acids.

Cognitive Effects of Omega-3 PUFA

In the nervous system as in all cells PUFAs can be released from membrane phospholipids when neurons are stimulated with neurotransmitters and can be metabolized in the brain giving rise to a series of a group of oxygenated C20 compounds, which include prostaglandins, thromboxanes, leukotrienes, and a variety of hydroxy and hydroperoxy fatty acids resolvins and protectins including neuroprotectin D_1 from DHA [62]. These products may act in the intracellular environment as neuronal secondary messengers and may be released in the extracellular space and interact with G-protein-coupled receptors on neurons and glial cells, thus influencing neuro-modulation, synaptic plasticity, and control of inflammation [62]. The PUFAs also have influence on cell migration and apoptosis [89, 90] contribute to synaptogenesis [91] and are involved in cholinergic, serotoninergic, and catecholaminergic transmission [91–93] and influence the length of telomeres. LA more than any other nutrient is associated with shorter telomeres and shorter telomeres are associated with aging, cancer and coronary heart disease [94, 95].

Animal studies have shown that omega-3's may play a role in cognitive development and omega-3 fatty acid deficiency impairs the ability to respond to environmental stimulation in rats, which suggests that the provision of omega-3's as well as omega-6's to the developing brain may be necessary for normal growth and functional development [96]. As omega-3 deficiency in rat brain has been associated with reduced biosynthesis of catecholamine and decreased learning ability, with a lower synaptic vesicle density in the hippocampus [97, 98] whereas chronic administration of omega-3's helps to improve reference memory-related learning [99] probably due to increased neuroplasticity of neural membranes [100]. Clinical studies show that cognitive performance improves with omega-3's [101] and different mechanisms have been proposed to explain this effect such as increased hippocampal acetylcholine levels [102], the anti-inflammatory effects of omega-3's, decreased risk of CVD or increased neuroplasticity [100].

On the basis of these mechanisms, positive effects of omega-3's on dementia, schizophrenia, and other central nervous system diseases have been reported [103, 104]. The description of effects on depression although controversial [105–108], has led to the conclusion that omega-3's can affect not only cognitive functions, but also mood and emotional states and may act as a mood stabilizer. Omega-3's have beneficial effects in some neurological diseases [109, 110] in addition to the chronic fatigue syndrome [111]. Both DHA and EPA appear to be necessary for these effects and this has been shown in depressive disorders [112]. Some controversial effects observed in depressive and schizophrenic patients may be related to DHA and EPA different functions or to differences in the AA/EPA ratios, since in many studies the ratio of omega-6/omega-3 has not been determined in the background diet. In a very important study on the effects of EPA and DHA in normal healthy adults, Fontani et al. showed that the addition of 2.8 g of EPA and DHA at a ratio of 2:1 led to a decrease in the AA/

EPA ratio after 35 days of supplementation without any changes in the control group (olive oil) from 14.26±8.87 before supplementation to 4.29±2.60 after supplementation [113]. The subjects underwent extensive neurophysiological testing including electroencephalogram and electromyogram. The profile of mood states showed significant changes. There was more vigor and less anger, anxiety, fatigue, depression and confusion in the supplemented group versus the control. The results of the experiments indicate a positive influence of omega-3 fatty acids on cognitive functions, while the decrease of the AA/EPA ratio could be considered confirmation of the biological effect of omega-3's, the changes in the reaction time and physiological parameters could be considered to be due to the effects of omega-3 fatty acids on the central nervous system. The possible mechanisms involved may be related to the fact that omega-3's act as a controller of neuronal excitability which influences protein kinases and thus protects the structure and function of the cell membranes [114]. Consequently, omega-3's can modulate many of the signal transduction mechanisms operating at the synaptic level [91]. Therefore, they may influence several pathways with different neurotransmitters such as serotonin, noradrenalin, dopamine and acetylcholine, which may explain their effects on learning, mood stability and other important cognitive functions [91, 97, 98, 102].

Childhood and old age are two critical and vulnerable periods when the supply of omega-3 PUFAs would be fundamental for a good brain functioning. In these periods, deficiency is associated with learning and memory deficits, sensory systems and mood. Furthermore, the deficiency in childhood might have delayed brain development, and produced irreversible effects, while the same deficiency in aging could entail acceleration in the deterioration of brain function.

An ongoing study on the relationship of the total diet to violence in prisoners showed multiple dietary deficiencies with 0% intake of selenium and omega-3 fatty acids from fish [115] (Table 5). The omega-3 intake from ALA in the presence of genetic variants in FADS1 and FADS2 will not be providing adequate intakes of EPA and DHA. This is an important area for further research to better understand the complex relationships of dietary intake, endogenous production of PUFA, the complex relationships between peripheral and central lipids play in the normative variability in effect, and psychopathology.

Omega-3's and Substance Abuse

Alcoholics are known to have poor diets and be deficient in omega-3 fatty acids, especially in DHA. However, the

Table 5 Diet of disaffection: nutrient intakes from a sample of disadvantaged young people

Nutrient	Percentage getting adequate intakes (%)	Possible effects of low intakes on the brain
B-12 Cobalamin	94	Pernicious anemia. Spinal cord damage. Raised homocysteine; this has been linked to CVS disease and hostility
B-6 Pyridine	83	Cofactor for conversion of tryptophan to serotonin (5-HT) and regulation of homocysteine. Depression. Alzheimer's
B-1 Thiamin	61	"Dry beriberi": peripheral neuropathy, Wernicke's and Korsakoff's encephalopathy. Reduced learning ability associated with impaired hippocampal neurogenesis in animal models
B-2 Riboflavin	33	Cofactor in electron transport chain, energy metabolism, and reduces ischemic brain injury
Iodine	33	Thyroid hormones–low intake of iodine is the commonest cause of mental deficiency worldwide
Folic acid	28	Methylation agent in synthesis of serotonin. Low intakes are associated with depression and raised homocysteine
Zinc	28	Found in over 100 enzymes, affecting membrane structure, neurogenesis, neurotransmitters, fatty acid metabolism. Low zinc intakes have been associated with ADHD and criminality
Calcium	28	Neural hyperexcitability, paresthesia, and impulsivity
Iron	22	Anemia. Also required for dopamine synthesis. Low iron is associated with impaired cognitive development in humans and aggression in animal studies
Magnesium	17	Involved in glycolysis and cerebral blood flow. Low intakes are associated with hyperexcitability and in animal studies with the severity of behavioral deficits
Selenium	0	Low intakes are associated with reduced cognitive function
Omega-3 from fish	0	Impaired attention, impulsivity, reduced memory, impaired cognition, depression, and excess inflammation

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deficiency of omega-3's is not limited to alcoholics. It is also found in poly-substance abusers but data are scan. Cocaine addicts have a high index of alcohol abuse (88%) and codependence (61%). The concurrent ingestion leads to the formation of cocaethylene, an active metabolite that seems to prolong and magnify the effects of cocaine. Chemical dependents (not only cocaine addicts) have poor eating habits and higher relapse rates and also have lower levels of total cholesterol and lower omega-3's especially the most aggressive participants. Omega-3's could be used as coadjuvants in the treatment of cocaine dependence and alcoholism since they can stabilize neuron membranes and act on the neural systems that were altered by the chronic use of these drugs, as well as by possible deficient or indadequate diets.

Substance abusers have been known to have low omega-3 fatty acid intake due to poor dietary habits. Because of the strong association between aggression, anxiety and substance use disorders Buydens-Branchey et al. [116] carried out a supplementation intervention study with 3 g of EPA and DHA with soybean oil as the control. The trial was double-blind, randomized and lasted 3 months. Anger and anxiety scales were administered at base line and once a month. The patient's dietary intake was below recommended levels. Daily administration of 3 g of omega-3's for 3 months significantly decreased feelings of anger and anxiety among substance abusers compared with the placebo group. Administration of omega-3's reduced the anxiety associated with the onset of craving, which is strongly connected to relapse. This decrease persisted for 3 months after treatment. There was a strong correlation between an increase in plasma EPA and lower end-of-trial anxiety scores and between an increase in plasma DHA and lower end-of-trial anger scores. There were strong associations between high frequency and high severity of aggressive behaviors and substance abuse disorders suggesting that an insufficient intake of omega-3's may be one of the factors contributing to increased violence in some individuals. An increase in DHA intake may increase plasma serotonin. The authors associated aggressiveness with impulsiveness and concluded that the levels of omega-3's were more important relapse predictors, than the previous pattern of drug abuse or clinical and sociodemographic parameters. This small short trial clearly showed that cursory adequate EPA and DHA intake through supplementation benefits substance abusers by reducing their anger and anxiety levels.

Conclusions and Recommendations

Western diets are characterized by high omega-6 and low omega-3 fatty acid intake, whereas during the Paleolithic period when human's genetic profile was established, there was a balance between omega-6 and omega-3 fatty acids. Therefore, humans today live in a nutritional environment that differs from that for which our genetic constitution was selected. Both omega-6 and omega-3 fatty acids influence gene expression. The balance of omega-6/omega-3 fatty acids is an important determinant in maintaining homeostasis, normal development, and mental health throughout the life cycle.

The types of fatty acids that are available to composition of cell membranes depend on diet and endogenous metabolism of LA and ALA. However, the critical factor in fatty acids efficacy is not their absolute level, but rather the ratio between various groups of fatty acids. It is known that the relative amounts of omega-6 and omega-3 in the cell membrane are responsible for affecting cellular function as the AA competes directly with EPA for incorporation into cell membranes. A low AA/EPA ratio has been proposed as an index of the beneficial effects of omega-3's which have been shown in animal and clinical experiments.

Animal studies have shown that omega-3's may play a role in cognitive development and their deficiency impairs the ability to respond to environmental stimulation in rats; indicating that the provision of omega-3 and omega-6 fatty acids to the developing brain may be necessary for normal growth and functional development. Omega-3 deficiency in rat brain is associated with reduced biosynthesis of catecholamines and decreased learning ability, with a lower synaptic vesicle density in the hippocampus; whereas, chronic administration of omega-3's improves reference memory-related learning probably due to increased neuroplasticity of the neural membranes.

Clinical studies indicate that cognitive performance improves with omega-3's supplementation possibly due to increased hippocampal acetylcholine levels, the anti-inflammatory effects of omega-3's, decreased risk of cardiovascular disease or increased neuroplasticity. Positive effects in patients with dementia, schizophrenia and other central nervous systems diseases have been reported. The effects of omega-3's on depression although controversial suggest that omega-3's affect not only cognition functions, but also mood and emotional states and may act as a mood stabilizer. The controversial effects observed in some depressive and schizophrenic patients may be related to DHA and EPA different functions or to differences in the AA/EPA+DHA ratios, since in many studies the omega-6/omega-3 ratio in the background diet has not been determined.

Alcoholics and drug abusers (cocaine) have poor diets with many nutrient deficiencies including omega-3 fatty acid deficiency. There is growing evidence that omega-3 fatty acid supplementation could play a role in hostility and

violence in addition to the beneficial effects in substance abuse disorders and alcoholism. The studies, so far, have been of small sample size, short duration and lack of information of the background diet relative to the omega-6 and omega-3 ratio. In carrying out clinical intervention trials, it is essential to increase the omega-3 and decrease the omega-6 fatty acid intake in order to have a balanced omega-6 to omega-3 intake in the background diet. Since blood levels of the omega-6 and omega-3 fatty acids depend on dietary intake and endogenous metabolism, genetic variation in the FADS1+FADS2 should be determined and red cell membrane or plasma phospholipids should be measured at baseline and during the clinical trial.

Because the enzymes involved in the metabolism of the LA and ALA are shared, there is competition between them, and the omega-3 and omega-3 fatty acids also regulate each other. The balance between LA and ALA and their (PUFA) metabolites in the diet is vital. In humans, the brain is the most outstanding organ in biological development: it follows that the priority is brain growth and development, and in the brain the balance between omega-6 and omega-3 PUFA metabolites is close to 1:1. This ratio should be the target for human nutrition. In Western diets, the omega-6/omega-3 ratio has increased to between 10:1 and 20:1. This high omega-6 proportion is largely made up by LA, is far from optimal and is highly inappropriate for normal growth and development. The ratio of omega-6/omega-3 fatty acids in the brain between 1:1 and 2:1 is in agreement with the data from the evolutionary aspects of diet, genetics, and the studies with the fat-1 animal model. Therefore a ratio of 1:1 to 2:1 omega-6/omega-3 fatty acids should be the target ratio for health.

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