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Chapter 12

Evolution and Therapy of Brain by Foods Containing Unsaturated Fatty Acids

Roberto Carlos Burini,

Caroline das Neves Mendes Nunes and

Franz Homero Paganini Burini

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Abstract

About 6 million years ago, our ancestors had experienced a tremendous brain growth, widely viewed as a "major adaptive shift" in human evolution. Half of human brain composition is fat and 20% of its dry weight is long-chain polyunsaturated fatty acids (LCPUFA). Consequently, improvements in consumption of dietary fat were necessary condition for promoting encephalization. Dietary fat quantity and quality have been subjected to tremendous change over the past 10,000 years with the introduction of industrially produced *trans* fatty acids and reduced intakes of ω-3 fatty acids. The *absolute human* brain size reached its peak of approximately 90,000 years ago and has decreased by 11% since 35,000 years ago, most of it (8%) coming in the last 10,000 years. The shortfall in consumption of animal foods since the late Paleolithic and mainly consequent shortfall in consumption of preformed LCPUFA would be the plausible hypothesis for the brain size decreasing. Genetically, we are still adapted to the East African ecosystem on which our genome evolved, with some adaptations since the Out-of-Africa Diaspora. Dietary fat quantity and quality change has caused a conflict with our slowly adapting genome and this mismatch is likely to be at the basis of "typically Western" diseases. Many recommendations for the intakes of EPA + DHA have been issued, notably for prevention. However, the ultimate goal might be to return to the fat quality of our ancient diet on which our genes have evolved during the past million years of evolution.

Keywords: human encephalization, LCPUFA sources, dietary transition, LPUFA in health, W-3/W-6 LCFA and modern diseases, therapeutical W-3 LCPUFA

1. Introduction

The evolution of Homo erectus in Africa is widely viewed as a "major adaptive shift" in human evolution. Humans share a common ancestor with the chimpanzee and bonobo that probably lived in East Africa and, since some 6 million years ago our ancestors had experienced a tremendous brain growth and assumed an upright position [1].

Half of brain composition is fat, but the central nervous system contains almost a quarter of the unesterified cholesterol present in the whole human body and, long-chain polyunsaturated fatty acids (LCPUFAs) make up to 20% of brain dry weight, including 6% for arachidonic acid (AA) and 8% for docosahexaenoic acid (DHA) [2].

2. Polyunsaturated fatty acids

LCPUFAs are building blocks of the membrane phospholipids of all cells. Nevertheless, LCPUFAs are not only important structural elements of membranes, together with their highly potent metabolites (prostaglandins, thromboxanes, leukotrienes, resolvins, and (neuro)protectins), LCPUFAs are involved in the functioning of membrane-bound receptors, transporters, ion channels, and enzymes, and also in signal transduction and gene expression.

LCPUFAs are ligands of nuclear transcription factors (PPARS, SREBPs, NF-kB, and others) [3–6] that coordinate expression and repression of key enzymes and proteins participating in intermediary metabolism in glycolysis and "*de novo*" lipogenesis, thermoregulation, energy partitioning, growth and differentiation, hemostasis, and (W-3/W-6 ratio) inflammatory responses [7–11].

3. Effect of diet on brain development

The anatomic trends of human evolution (large body sizes, bigger brains, craniofacial, and intestinal changes) clearly suggest major energetic and dietary shifts [12–14].

Improvements in dietary quality and the increased consumption of dietary fat appear to have been a necessary condition for promoting encephalization in the human lineage [15].

Primitive humans with enlarging brains developed more sophisticated tool technology (including the fire cooking) and became more efficient hunter/gatherers and so gained greater access to more nutritious and easily digestible foods (e.g., fruits, nuts, and meat) [11].

Consequently, reductions of posterior tooth size (and grinding teeth) and, also the size of the face and so, no longer needed the large gastrointestinal tract. Key genetic mutations during later hominid evolution were critical to promoting the enhanced lipid metabolism necessary for subsisting on diets with greater levels of animal material [16].

In fact, associated with the evolution of our high-quality diet, humans developed distinct molecular pathways for detecting and metabolizing high-fat foods [17].

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The ability to effectively detect, metabolize, and store fats likely provided tremendous selective advantages to our hominid ancestors, allowing them to expand into diverse ecosystems around the world [18].

Mammalian brain growth is dependent upon sufficient amounts of two LCPUFAs: DHA and AA [19].

It appears that mammals have a limited capacity to synthesize these fatty acids from dietary precursors. Because the composition of all mammalian brain tissue is similar with respect to these two fatty acids, species with higher levels of encephalization have greater requirements for DHA and AA. Consequently, dietary sources of DHA and AA were likely limiting nutrients that constrained the evolution of larger brain size in many mammalian lineages [18].

On average, we consume higher levels of dietary fat than other primates, and much higher levels of key LCPUFAs are critical to brain development [20, 21].

Hominins had experienced a tremendous brain growth which coincided with a change from a vegetarian to a hunting-gathering omnivore-carnivore [22–25].

Greater consumption of animal foods would have increased total dietary fat consumption in early Homo, and markedly increased the levels of key fatty acids (AA and DHA) necessary for brain development. The available evidence seems to best support a mixed dietary strategy in early Homo that involved the consumption of larger amounts of animal foods than with the australopithecines. Brain tissue is a rich source of both AA and DHA, whereas liver and muscle tissues are good sources of AA and moderate sources of DHA [18].

Dietary fat quantity and quality have been subjected to tremendous change over the past 10,000 years. Important changes are the introduction of manufactured linoleic acid (LA), trans-fatty acids, and reduced intakes of vegetal-derived alpha-linolenic acid (ALA) and fish-derived eicosapentaenoic acid (EPA) and DHA, overall leading to a reduced supplying of omega-3 fatty acids [11].

Analysis of changes in brain size in humans over the last 1.8 million years found that encephalization quotient (EQ) began reaching its peak with the first anatomically modern humans of approximately 90,000 years ago and has since remained fairly constant. Most surprisingly, however, absolute brain size has decreased by 11% since 35,000 years ago, with most of this decrease (8%) coming in just the last 10,000 years. Therefore, a genetic mutation is no more likely as an explanation for the decrease in absolute brain size. The most notorious dietary change in the last 10,000 years has been the decreased consumption of animal food (roughly from 50 to 10%) by the adventure of agriculture, followed by an increased consumption of grains. Hence, the most feasible biological hypothesis for the absolute decrease in brain size is the reduction of animal food intake with a consequent reduction of preformed long-chain fatty acids. The brain is dependent on the DHA, docosatetraenoic acid (DTA), and AA to support its growth during the formative years. These are far more plentiful in animal foods than plant. It is possible that the levels of essential fatty acids (EFAs) provided in the prehistoric diets were sufficient to support the brain expansion and evolution from prehistoric times to the present, and the current low levels of EFA intake (provided by agricultural diets) may explain the recent smaller human brain size [26].

4. Transition of diet and the development of brain disease

Dietary fat quantity and quality change have, together with other man-made changes in our environment, caused a conflict with our slowly adapting genome [11].

In fact, the EFA and other changes in our diet together with an energy intake that does not match with our current sedentary lifestyle have caused a conflict with our genome that is likely to be at the basis of typically "Western" diseases and their basis on the conflict (mismatch) caused by our current sedentary-energy rich industrialized diet, way of life with our ancestrally molded genome. The dietary composition of our ancestors has also become clear from our current (patho)physiology: epidemiological data demonstrated a negative association of fish consumption with coronary artery disease (CAD) and (postpartum) depression, while landmark trials with ALA and fish oil in CAD, and with EPA in depression and schizophrenia supported the causality of these relations.

The similarity among diseases currently associated with dietary risk factors adds the notion that there is a common insult originated from our changed environment. These effects hit different organs and systems varying in genetic susceptibility and life stages, but extremely dependent on the doses and exposure time. Low-grade inflammation might be a strong candidate for this common denominator. Low-grade inflammation can be found in metabolic syndrome and its sequelae, some psychiatric and neurodegenerative diseases. The LCPUFA, AA, EPA, and DHA are intimately related to the initiation and resolution of inflammatory responses [11].

The current balance between AA and EPA + DHA is disturbed by the dominance of AA, which originates from the diet or synthesis from LA. Higher ratio of AA/EPA+DHA might led to a pro-inflammatory condition that may precipitate a hyper-inflammatory response ("systemic inflammatory response syndrome-SIRS") with collateral damage, scarring and fibrosis and the subsequent development of an immune paralysis ("compensatory anti-inflammatory response syndrome-CARS") evidenced by debilitated host defense and secondary infection susceptibility [27, 28].

The chronic inflammation resulting from the unbalanced AA/EPA + DHA ratio might be central in the pathogenesis of the diseases of the metabolic syndrome and neurodegenerative disease, explain the relation between inflammation, depression, and dementia [29].

5. Therapy of modern diseases with polyunsaturated fatty acids

Dietary supplementation of LCFA, especially EPA and DHA, has been used during pregnancy or early postnatal life for improvement of fetal and newborn brain development, at primary and secondary CAD preventions and psychiatric diseases. Consensus has been reached that those in CAD and depression are positive but not in all others. LCPω3 supplements might especially be effective in prevention, as suggested by the outcomes of epidemiological studies on CAD and prospective studies on Alzheimer's disease, and also from the favorable effects of LCPω3 in early disease stages [30].

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It takes 20 years before the human brain obtains its complex adult configuration but the most dramatic neurodevelopmental changes occur prenatally and early post-natal, including a major transformation in cortical organization 3–4 months after term and, considerable evidence indicates that prenatal and neonatal LCPUFA status is associated with neurodevelopmental outcome. Therefore, maternal and neonatal concentrations of DHA and AA are associated with improved outcomes in early infancy, and concentrations of DHA are associated with favorable neurodevelopmental outcome beyond early infancy [31].

Given the fact that LCPUFA accretion is especially abundant during the third trimester of gestation, it suggests that preterm infants would particularly profit from LCPUFA supplementation. However, studies of LCPUFA supplementation in preterm infants have not shown evidence of a positive effect on neurodevelopmental outcome. On the other hand, studies in full-term infants indicated that DHA supplementation promotes neurodevelopmental outcome in early infancy but no longer positive effects later on, being virtually absent at school age or later. Generally, the literature suggests that LCPUFA supplementation in term infants does not affect outcomes beyond the age of 4 months [31].

It is known that up to 45% of the fatty acids of synaptic membranes are EFAs [32].

There is a well-established positive correlation between depression and coronary artery disease. In fact, epidemiological studies in various countries suggest that decreased ω-3 fatty acid consumption correlates with increasing rates of depression and, adequate long-chain polyunsaturated fatty acids, particularly DHA, may reduce the development of depression just as ω-3 polyunsaturated fatty acids may reduce coronary artery disease [33].

Eight database trials that randomly assigned participants to receive ω-3 PUFAs/fish, with measured depressed mood, using human participants, came to the conclusion that trial evidence of the effects of ω-3 PUFAs on depressed mood has increased. However, the considerable heterogeneity of the studies made them difficult to summarize the results. Overall, the available evidence supports the benefit of ω-3 PUFAs in individuals with diagnosed depressive illness but no evidence of any benefit in individuals without a diagnosis of depressive illness [34].

The association between fish and meat consumption and risk of dementia in populations in developing countries was investigated in low- and middle- income countries of China, India, Cuba, the Dominican Republic, Venezuela, Mexico, and Peru. The found associations of fish and meat consumption with dementia risk to populations were consistent with mechanistic data on the neuroprotective actions of ω-3 PUFAs commonly found in fish. However, the inverse association between fish and prevalent dementia is unlikely to result from poorer dietary habits among demented individuals (reverse causality) because meat consumption was higher in those with a diagnosis of dementia. But anyway, the found beneficial effects of fish consumption on dementia provide preliminary evidence of the etiological significance of diet in dementia [35].

Given the fact that PUFAs are naturally occurring endogenous substances, present in almost all tissues and are essential components of all mammalian cells and can be taken safely for long periods of time (from few months to few years) we can conclude that PUFAs, especially ω-3 fatty acids, are useful in the prevention and treatment of Alzheimer' disease, schizophrenia, and depression [36].

The pioneering studies in Greenland Eskimos almost 30 years ago suggested that ingestion of *n*-3 fatty acids conveys protection from cardiovascular diseases [37].

Since then, many interventions have been conducted with LCPUFA, especially EPA and DHA, aiming at primary and secondary CAD preventions. From that, in most of the prospective cohort studies, *n*-3 fatty acids were found to be beneficial [38–43] but there were also exceptions with no effect [44, 45].

By comparing people who never or ate fish less than once per month, a meta-analysis of 11 prospective studies (11.8 years follow-up of more than 220 thousand subjects) showed the odds ratio for CHD mortality as 0.85 for fish consumption once per week, 0.77 for 2– 4 times/week, and 0.62 for 5 times/week. The authors calculated that each 20 g/day increase in fish intake was associated with a 7% lower risk of coronary heart disease mortality [46].

Many international organizations have made recommendations to increase the intake of EPA plus DHA, and these are summarized by the International Society for the Study of Fatty Acids and Lipids [47]. In general, these recommendations are for 200 mg/day of EPA plus DHA for all adults. The United States has also issued a Dietary Reference Intake for *n*-3 fatty acids [48].

The 2002 American Heart Association recommendations for dietary intake of *n*-3 fatty acids recommended: (1) in the absent of documented CHD it is advised to eat fish twice per week plus oils and foods rich in ALA (flaxseed, canola, soy, walnuts), this accomplishes 500 mg/day of *n*-3 fatty acids. (2) Individuals already with CHD are advised to eat 1 g/day of EPA plus DHA, preferably from oily fish, but could take EPA plus DHA supplements. (3) Individuals with hypertriglyceridemia could take 2–4 g/day of EPA plus DHA, under prescription care [49].

Several mechanisms have been proposed to explain how EPA plus DHA might beneficially influence cardiovascular disease. These include preventing arrhythmias, lowering plasma triacylglycerols, decreasing blood pressure, decreasing platelet aggregation, improving vascular reactivity, and decreasing inflammation. Overall, the therapeutic effect appears to be due to suppression of fatal arrhythmias rather than stabilization of atherosclerotic plaques [50–60].

Elevated plasma triacylglycerol concentrations have been associated with increased risk of coronary heart disease (CHD). Prospective evidence shows that nonfasting plasma triacylglycerol concentration is a strong and independent predictor of future myocardial infarction once elevated postprandial triacylglycerolemia leads to a series of metabolic reactions that reduce high-density lipoprotein (HDL)-cholesterol concentrations and promote the formation of small, dense low-density lipoprotein (LDL) particles. Metabolism of plasma triacylglycerols also influences postprandial factor VII activation [61].

EPA and DHA are *n*-3 PUFAs in fish oil which are effective hypotriacylglycerolemic agents, even when consumed at low doses (1 g *n*-3 PUFA/d). Therefore, consumption of *n*-3 PUFAs provides a realistic option for the optimization of plasma triacylglycerol metabolism [61].

Omega-3 fatty acid supplementation provided additional benefits to Lifestyle Modification Program (LSMP) in the resolution of metabolic syndrome of free living adults. The fish oil group received 3 g of fish oil per day (360 mg of DHA and 540 mg of EPA) (G2, $n = 23$)) during 20 weeks. Compared to the control group (only LSMP) the intervened group showed a significant decrease in waist circumference (1.3%) followed by metabolic syndrome reduction (29%) mainly due to normalization of blood pressure (33.3%) and triacylglycerol (27.3%). Some theories have been proposed to explain how omega-3 reduces triacylglycerol. The strongest evidence is the reduction in hepatic lipogenesis, reducing hepatic secretion of very low-density lipoprotein (VLDL). Additionally, omega-3 inhibits certain enzymes involved in the hepatic synthesis of triacylglycerol, reducing its plasma level [62].

A significant decrease of plasma oxidative-stress markers in patients with ulcerative colitis was shown when fish oil ω-3 fatty acids were used in combination with sulfasalazine [63].

Regarding type 2 diabetes mellitus (T2DM), a prospective cohort analysis of men and women showed that long-term dietary intake of long-chain omega 3 fatty acids does not decrease the risk of T2DM. Instead, a modestly but significantly higher incidence of T2DM was associated with higher fish and long-chain omega 3 fatty acid consumption [64].

Doses 3 g/day, EPA plus DHA can improve cardiovascular disease risk factors, including decreasing plasma triacylglycerols, blood pressure, platelet aggregation, and inflammation, while improving vascular reactivity [50].

By the fact that EFAs and their long-chain metabolites and other products prevent platelet aggregation, lower blood pressure, reduce LDL-cholesterol, and ameliorate the adverse actions of homocysteine, the EFAs and their metabolites show all the actions expected of the "polypill" [65].

The concept of cardiovascular "polypill" was coined [66] by the fact that, when combined, the effects of statins, aspirin, and blood pressure lowering drugs reduced the all causes mortality in CHD patients.

In conclusion, it is evident that PUFAs, especially an optimal combination of EPA, DHA, and possibly, gamma-linolenic acid (GLA), dihomo-gamma-linolenic acid (DGLA), and AA show all the qualities of the suggested "polypill", viz., aspirin-like action, inhibition of HMG-CoA and angiotensin-converting enzymes (ACEs), and possess diuretic, antihypertensive, and beta-blocker-like actions. Additionally, given the fact that PUFAs are naturally occurring endogenous substances, present in almost all tissues and are essential components of all mammalian cells and can be taken safely for long periods of time (from few months to few years), we can conclude that PUFAs, especially ω-3 fatty acids, are useful in the prevention and treatment of Alzheimer' disease, schizophrenia, and depression [36], suggesting that PUFAs have a much wider benefit compared to the "polypill" [65].

Thus, LCPω3 supplements might especially be effective in prevention, as suggested by the outcomes of epidemiological studies on CAD and prospective studies on Alzheimer's disease, and also from the favorable effects of LCPω3 in early disease stages [30]. Consensus has been reached that those interventions in CAD and depression are positive but not in all others.

6. Future directions

Genetically, we are for the greater part still adapted to the East African ecosystem on which our genome evolved, with some adaptations since the Out-of-Africa Diaspora. Dietary fat quantity and quality change have, together with other man-made changes in our environment, caused a conflict with our slowly adapting genome that is implicated in "typically Western" diseases. Fortunately, the majority of Western diseases occur typically after reproductive age. Rather than reducing our life expectancy, these diseases notably diminish our number of years in health.

Many recommendations for the intakes of saturated fat, *trans* fat, and EPA + DHA have been issued, notably for prevention. The ultimate goal might be, however, translate to the culture of the current society that our genes had evolved for million years in an entirely different dietary composition and lifestyle and therefore we must return to the fat quality of our ancient diet [11].

Author details

Roberto Carlos Burini[1]*, Caroline das Neves Mendes Nunes[2] and Franz Homero Paganini Burini[3]

*Address all correspondence to: burini@fmb.unesp.br

1 Public Health Department, UNESP Medical School, Botucatu, Brazil

2 Pathology Department, UNESP Medical School, Botucatu, Brazil

3 UNESP Medical School Clinical Hospital, Botucatu, Brazil

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