Is Docosahexaenoic Acid (DHA) Essential? Lessons from DHA Status Regulation, Our Ancient Diet, Epidemiology and Randomized Controlled Trials

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The human diet has changed considerably during the last 100 y. One of the striking changes is the tremendous increase in dietary fat. In terms of quality we have increased our intakes of saturated fatty acids (SFA),[2] linoleic acid (LA) and *trans*-fatty acids, concomitant with reduced intakes of (n-3) fatty acids. The latter comprises reduced intake of α-linolenic acid (ALA) rich foods, and less consumption of long-chain PUFA of the (n-3) series [LC(n-3)P], i.e., eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids notably from fish (1). These dietary and other environmental changes are considered to be among the major causes of the rapid expansion of diet-related chronic disease (2), including cardiovascular disease (CVD) in the past century. Our genetic constitution is unlikely to have kept pace with the changing diet. Today's nutritional habits are consequently not the same as those on which our genes are based (2). The return to basics may be indicated, but we unfortunately have no reliable knowledge of the ancient diet on which our genes evolved. In this literature study we seek to find whether LC(n-3)P, and notably DHA, are essential.

Essential fatty acid (EFA) metabolism and function. The parent essential fatty acids (EFA), LA and ALA cannot be synthesized in the human body and are therefore indispensable components of our diet. Both LA and ALA may be converted by chain elongation, desaturation and chain-shortening into their respective long-chain metabolites, collectively named LCP ($\geq$20 carbon atoms and $\geq$3 double bonds). The most important LCP of the (n-6) fatty acid series is arachidonic acid (AA), whereas EPA and DHA are the major LC(n-3)P. LCP may also be derived from the diet. High contents are present in meat (AA) and fish (EPA, DHA). AA and DHA are especially abundant in the brain and the retina. Both LCP and their parent precursors may serve for energy generation, but LCP are relatively protected from β-oxidation compared with their parents. AA and DHA are important building blocks of structural lipids. LCP in phospholipids contribute to membrane properties like fluidity, flexibility, permeability and modulation of membrane-bound. DHA in retina and postsynaptic membranes is crucial for adequate functioning of embedded proteins, i.e., rhodopsin for vision and postsynaptic receptors for neurotransmission. AA, EPA and dihomo-γ-linolenic acid (DGLA), liberated from membrane phospholipids, are precursors of short-lived highly potent regulatory hormones collectively named eicosanoids. These play important roles in inflammatory reactions, blood pressure control and platelet aggregation. Eicosanoids from AA are involved in vasoconstriction/platelet aggregation (TxA_2), inhibition of vasodilatation/platelet aggregation (prostaglandin I_2), inflammation, and leukocyte chemotaxis and adhesion. EPA and DGLA compete with AA for eicosanoid synthesis. The eicosanoids of EPA (e.g., PGI_3) and DGLA are generally less potent and may thereby change the balance towards attenuated inflammation, platelet aggregation and vasoconstriction. PUFA, LCP and their derivatives are of increasing interest as modulators of gene expression ("diet-gene interaction"). They are, for example, ligands of peroxisome proliferator activated receptors (PPAR) (3) and suppressors of sterol regulatory element binding proteins (4). These are nuclear transcription factors at the crossroads of metabolic control, cholesterol homeostasis and inflammation. PPAR-β/δ is implicated in growth and development (5).

Evidence from regulation of AA and DHA status. In contrast to AA, our DHA status seems rather sensitive to the fluctuation of dietary intakes. Both circulating and human milk AA contents are subject to relatively low interindividual biological variation, but the interindividual variations of both EPA and DHA are among the highest (6,7). Vegans and omnivores have little difference in AA status, but remarkably different DHA status (6). These data are in line with AA (8–10) and DHA (11–13) supplementation studies showing that the AA contents of plasma-free fatty acids, plasma triglycerides, platelets, erythrocytes, adipose tissue and milk are not easily changed, but that the intake of fish or fish oil supplements readily increases the EPA and DHA contents of a variety of compartments, including milk. In some cells (e.g., erythrocytes) AA becomes easily replaced by LC(n-3)P (12). However, cells in which AA appears to have important functions [e.g., platelets; (14)] are remarkably resistant towards AA

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[2] Abbreviations used: AA, arachidonic acid; ALA, α-linolenic acid; CVD, cardiovascular disease; DGLA, dihomo-γ-linolenic acid; DHA, docohexaenoic acids; EFA, essential fatty acids; EPA, eicosapentaenoic acids; LA, linoleic acid; LCP, long-chain PUFA; PPAR, peroxisome proliferator activated receptor; SFA, saturated fatty acids.

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replacement. AA and DHA surpluses become distributed differently among the body's lipid classes. EPA and DHA may be incorporated into both phospholipids and adipose tissue triglycerides (12), but this is much less the case for AA (10). An AA surplus is notably to be found in phospholipids, either as AA or its chain elongation product 22:4(n-6) fatty acid (10). The storage of AA in phospholipids and not triglycerides might protect us from the unregulated release of free AA by the activity of hormone sensitive lipase and indeed the AA content of plasma-free fatty acids is only marginally altered after AA supplementation (10).

In contrast to the ease by which DHA status is influenced by dietary intake, it has become clear that humans are rather poor DHA synthesizers. This notion comes from studies showing the following:

- Higher LCP contents in fetal than in maternal circulation ["biomagnification" (15)] suggests that nature has determined a major role for transplacental transport and to a lesser extent fetal LCP synthesis.
- The poor conversion of labeled ALA to DHA, but not to EPA and its elongation product 22:5(n-3), in young men, but better conversion to DHA in women of childbearing age (16–18) suggests that the DHA synthesis machinery becomes somewhat upregulated in conditions of high DHA demands.
- The relation between fetal and maternal LCP status and depletion of maternal stores during pregnancy and lactation suggests that the maternal diet should contain higher LCP contents (19).
- The LCP status of newborns is lower in those receiving formula with LA and ALA, but not LCP, compared with counterparts receiving human milk or formula with LCP (20,21).
- The predominant β-oxidation of orally administered stable isotopically labeled parent EFA is opposed to the predominant tissue incorporation of orally administered LCP (22–24).
- The inability of dietary ALA supplements to augment DHA status in vegans has been observed despite their low baseline DHA status (25).
- A highly increased EPA and its elongation product, 22:5(n-3), with DHA within the reference range, follows the administration of 12 g ethyl-EPA daily for 16 mo (14).

It seems that body AA status is well regulated with respect to magnitude and the safety of the AA storage form. This is not the case for DHA, and also ALA to DHA conversion proceeds with difficulty. The difficulty tracks down to the conversion of 22:5(n-3) to DHA. The concept emerges that at least some LCP might be conditionally essential to humans, or perhaps essential, as in the obligate carnivorous cat. Some of us, like the Inuits, may have even more difficulty synthesizing LCP because of long-standing predominantly carnivorous diet (26). A consistently high dietary LCP intake by our hominid ancestors might have precluded the need to conserve a highly sophisticated expression machinery of genes coding for the enzymatic conversion of ALA to DHA. In other words, there might not have been a need to regulate DHA levels if our ancient diet was consistently rich in DHA.

Evidence from our presumed ancient diet. DNA sequence comparisons indicate that the divergence of human and gorilla lineages dates back to 8.3–10.1 million years and that the most recent divergence with great apes was with the chimpanzee about 5.8–7.1 million years ago (27). The disparity between human and chimpanzee genomes is nevertheless estimated to be no more than 1.24% (28). Among the most noticeable consequences of these genomic differences are our upright posture and less abundant hair, but also the size of our skull holding a brain of about 1300 g compared with a 450-g counterpart in the chimpanzee. Studies of the fossil remains of our hominid ancestors indicate that during this evolution our diets have changed substantially. The size and teeth of hominid jaws became more typical of carnivores and omnivores, while the initially large pyramid-shaped thorax, characteristic for the accommodation of the large gut of a predominantly vegetarian primate, became gradually modified into a more cylindrical shape that usually surrounds the smaller gut of a carnivore. Conserved bones of butchered animals, as well as isotopic analysis of hominid bones, support the contention that during evolution our diets must have changed from predominantly vegetarian to that of an omnivore (29).

It is as yet unclear what enabled us to expand our brains during evolution. About 60% of our brain dry matter is lipid, and AA and DHA are among the most abundant fatty acids of brain phospholipids (30). This raises the question as to how we have been able to meet the increasing LCP demand. Future elucidation of the 1.24% difference of our genome with that of chimpanzees will undoubtedly provide us with at least part of the answer, and many candidate genes either involved in LCP transport, binding or metabolism have already been postulated (29). Regarding the origin of the LCP there is little doubt, because they derive either directly from the diet or become synthesized from LA or ALA. As outlined above, predominant derivation from synthesis seems unlikely, but if we need LCP from the diet, what did our ancestors eat to support a brain growth from 450 to 1300 g. African hominids have long been assumed to have been hunter-gatherers who obtained a great deal of their food from the open savanna. Meat from savanna animals is a poor DHA source, but savanna meat does have higher (n-3)/(n-6) ratios compared with domestic animals (31). Savanna hunting is, however, not easy even with modern tools. Hunting hominids at that stage of human evolution would have possessed unimaginable complex cognitive functions for planning, stalking, coordinating and communication (29). It is more likely that they lived at the margins of lakes and rivers or at the seashore because that is where most of their remains and tools have been discovered. Examples of these locations are to be found in the East African Rift Valley, e.g., lake Turkana in the present Kenya (e.g., "Turkana boy," a *Homo erectus*), but also in the South African Cape and the Central African Chad Basin (32). From these breeding nests of the new hominid species they may have spread in at least three "out of Africa" waves to colonize the entire world (33). "We may have to trade the picture of our African ancestors from a brawny hunter who brings home the wildebeest to butcher it with stone tools into that of a fisherman who wades the placid lakes and comes home with easily caught fish, seabird eggs, mollusks and other marine foods" (34). Many fishes from tropical warm waters, including those in lakes Nyasa and Turkana (31), are rich sources of AA and DHA, as opposed to their EPA- and DHA-rich counterparts from the more Northern climates.

Taken together, it is conceivable that we are poor DHA synthesizers and that the ancient diet was rich in LC(n-3)P, but that does not necessarily imply that higher LC(n-3)P would be needed to prevent any contemporary adverse effects. The low LC(n-3)P synthesis rate may still provide us with a sufficient LC(n-3)P status. Whether this is the case should be determined by epidemiological observations and intervention studies.

Evidence from epidemiology and randomized controlled trials. Low (n-3) intakes, (n-3) status or (n-3)/(n-6) fatty

acids ratios are epidemiologically related to CVD, inflammatory disorders, and mental and psychiatric diseases such as attention deficit disorders, dyslexia, dementia (postnatal) depression and schizophrenia (35–38). Epidemiological data cannot provide us with proof of causality, but the first results of randomized interventions have been convincing and many will probably follow. Secondary prevention trials with ALA in France (39) and fish oil in Italy (40) indicate reduced mortality from CVD (notably cardiac arrhythmia), whereas the administration of ethyl-EPA to patients with unipolar depression reduces Hamilton depression scale scores (41). Analogous relations have not as yet been demonstrated in subjects consuming vegetarian diets with low LC(n-3)P contents. These subjects have a 24% lower risk of ischemic heart disease, but not of other mortality causes, when compared with omnivorous counterparts. This difference is thought to be mainly due to higher intakes of fruit and vegetables, less smoking and higher physical activity (42). It is unknown whether increased LC(n-3)P intakes decrease their CVD risk or risk of other diseases, although it has been shown that it reduces their high platelet aggregation and total cholesterol/HDL-cholesterol and LDL-cholesterol /HDL-cholesterol ratios (43,44).

Low LC(n-3)P intake in the neonatal period is causally related to (transient) suboptimal neurodevelopment. Human milk contains LCP, whereas classic infant formulas do not. Both the intrauterine and neonatal periods are characterized by high LCP needs, and there is biochemical evidence that these needs cannot be met fully by neonatal LCP synthesis from LA and ALA (45,46). LCP may therefore be conditionally essential in the early postnatal period when the brain reaches its highest growth rate. This is supported by numerous randomized controlled trials with preterm and term infant formulas with and without LCP, using human milk as a reference. These trials revealed that formula without LCP cause biochemically demonstrable low LCP status in various body compartments, including the brain [notably DHA (47)], and that LCP-enriched formulas augment LCP levels to reach those of breastfed infants. The biochemical differences coincide with different neurodevelopmental stages, notably of preterm infants, during the first four postnatal months, as demonstrated by various tests of visual, perceptive, cognitive and motor development (45,48). Helland et al. (49) reported higher IQ at the age of 4 y in term infants supplemented with LC(n-3)P during pregnancy and lactation. Forsyth et al. (50) found lower blood pressure (diastolic pressure in particular) at the age of 6 y in term infants fed LC(n-3)P + LC(n-6)P during the 1st 4 mo of life. At present there is consensus regarding the addition of LCP to formulas of preterm infants (20). LCP supplementation of formulas for term infants has gained increasing support and various nutritional committees have issued recommendations for the LCP contents of formulas derived from the human milk fatty acid composition as the standard. Because there is little regulation of human milk DHA content apart from its maternal dietary content, and because of the low (n-3) fatty acid contents and (n-3)/(n-6) fatty acids ratios of the current Western diet, one may question whether the contemporary human milk DHA content may serve as a standard.

CONCLUSIONS

Human beings are poor DHA synthesizers, possibly because of their LC(n-3)P-abundant ancient diet. Dietary changes in the past century have lowered the (n-3) status to a current state of subclinical deficiency that is epidemiologically related to CVD, inflammatory disorders, mental and psychiatric diseases and suboptimal neurodevelopment. The strongest evidence comes from randomized controlled trials with LC(n-3)P, showing reduced mortality from CVD, improved neonatal neurodevelopment, and lower blood pressure in later life. With these studies as evidence, we conclude that DHA is likely to be essential.

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