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Long chain omega-3 fatty acids: Micronutrients in disguise ☆

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ABSTRACT

Considerable information has accumulated to show that DHA and EPA have unique roles that differ from other n-3 fatty acids and the n-6 fatty acids, with increasing understanding of the mechanisms through which these fatty acids reduce risk of disease. DHA and EPA regulate hepatic lipid and glucose metabolism, but are present in foods of animal origin, which are generally high in protein with variable triglycerides and low carbohydrate. Biological activity at intakes too low to provide significant amounts of energy is consistent with the definition of a vitamin for which needs are modified by life-stage, diet and genetic variables, and disease. Recent studies reveal that DHA may play a central role in co-coordinating complex networks that integrate hepatic glucose, fatty acid and amino acid metabolism for the purpose of efficient utilization of dietary protein, particularly during early development when the milk diet provides large amounts of energy from fat.

1. Introduction

It is increasingly recognized that dietary fatty acids provide not only a source of energy, but also have diverse structural and functional roles. Critical to understanding the links between dietary fatty acids and human health is the appreciation that fatty acids are structurally, metabolically and functionally diverse, both between and within classes of n-6 and n-3 polyunsaturated fatty acids. Thus, fatty acid carbon chain length, and the position and number of double bonds dictate what in many cases, are highly regulated roles and metabolic fates, for example oxidation for energy, acylation in triglycerides, phospholipids, sphingo- and other lipids, as well as metabolism by lipoxygenases, cyclooxygenases or to acylated molecules that function in cellular communication and regulation. Diets rich in the long chain n-3 fatty acids, eicosapentaenoic acid (20:5n-3, EPA) and docosahexaenoic acid (22:6n-3, DHA) are associated with decreased risk of cardio-metabolic and inflammatory diseases, loss of neurological potential and several mental disorders [1–8]. Unlike common 14–18 carbon chain fatty acids, DHA and EPA are poor substrates for mitochondrial and peroxisomal β-oxidation [9,10], but also have distinctly different roles from one another.

Much of the interest in DHA in early development has focused on the brain and retina, explained by the high amounts of DHA, but not EPA in brain gray matter and the retina rods and cones [11–13], and functional importance of DHA in these tissues [13–16]. However, dietary patterns that compromise DHA accretion in the developing brain and retina also reduce DHA in the liver [17–20], which is of concern due to the central role of the liver in glucose, fatty acid and amino acid metabolism, and known actions of fatty acids in regulation of gene expression [21,22]. This paper describes recent work to highlight that in the diet, DHA intake is fundamentally linked to animal protein, with biological activity at intakes so low as to be insignificant as sources of fat or dietary energy [25]. This is followed by recent work aimed at unraveling a role for DHA as a micronutrient that facilitates efficient use of glucose carbons and amino acid nitrogen for healthy growth and development in the young infant consuming a high fat milk [26,27].

2. Dietary distribution and supplies of n−3 fatty acids

As is well known, though perhaps not fully appreciated, the amounts and food sources of 18:2n-6 and 18:3n-3 compared to DHA, EPA and arachidonic acid (ARA, 20:4n-6) are strikingly different. Linoleic acid (18:2n-6) and 18:3n−3 are biosynthesized via the plant microsomal Δ12 desaturase and Δ15 desaturase, respectively, both of which are absent in mammalian cells. In contrast, DHA and EPA are synthesized from 18:3n-3, and ARA is synthesized from 18:2n-6 via the microsomal Δ6 and Δ5 desaturases which are present in mammalian, but not plants cells. As such, the major food source of 18:2n-6 and 18:3n-3 in modern diets

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is refined vegetable oils, both directly and indirectly in processed foods. Intakes of 18:2n-6 and 18:3n-3 is in gram quantities with US dietary guidelines recommending 6–10% dietary energy [27,28], equivalent to about 13–22 g/day from 18:2n-6 in a 2000 kcal diet. DHA and EPA are consumed in mg quantities, with recommended intakes of 200–500 mg/day EPA plus DHA [29,30] equivalent to only 0.09–0.22% energy in a 2000 kcal diet. Human milk provides variable, but low DHA ranging from 0.06 to 1.4% of milk fatty acids, with much of this variation explained by differences in the mother's intake of DHA [31–33]. Assuming 50% energy from fat in human milk, the breast-fed infant consumes well under 1% daily energy as DHA, compared to intakes of 18:2n-6 typically exceeding 5% of energy, i.e. over 10% of human milk fatty acids [32,33]. Regardless, even at intakes which are negligible as sources of energy, DHA and its precursor EPA are positive modulators of health and disease risk across the lifespan [1–8], with definitive effects on hepatic metabolism as evidenced by lowering of plasma triglycerides and hepatic secretion of apo B containing very low density lipoprotein (VLDL) [34–38]. Numerous studies have shown that even small amounts of DHA lead to relatively large increases in DHA in blood and tissue lipids in adults and infants. For example, healthy adult men given 0.2% energy/day DHA (600 mg) for 2 weeks showed a 50% increase in plasma phospholipid DHA from 2.2% to 3.4% fatty acids [39], while infants given 0.22% DHA in their formula fat (62 mg/day DHA, equivalent to about 0.1% dietary energy) showed a similar increase in plasma phospholipid DHA from 2.7% to 3.2% fatty acids [40].

Since the desaturase enzymes needed to form DHA from 18:3n − 3 are found in animal cells and a few single celled organisms, DHA is naturally present in human diets only in association with animal lipids, unless modified by biotechnology or fortification. The highest concentrations of DHA are in fish, marine mammals and other seafood, as well as non-ruminant muscle and organ meats, and eggs. Thus DHA is in foods that primarily provide protein, with varying and sometimes low amounts of triglyceride, and uniformly low carbohydrate. For e.g., 100 g salmon with 700 mg DHA also has 27 g protein, about 50% of the current dietary reference intake for protein of 56 g/day for adult men and 46 g/day for adult women [27]. Analysis of the diets of 611 Canadians, over a wide age range of 1.5–65 years, showed that DHA (and EPA) intake increased with increasing protein ($P < 0.001$), but not fat intake ($P > 0.05$) [24]. In contrast, intakes of 18:2n − 6 and 18:3n − 3 increased with increasing fat intake ($P < 0.001$), with no association to protein intake ($P > 0.05$). Among this group of Canadians, EPA and DHA provided a mean of 0.07% dietary energy, with a 5th to 95th percentile range of intakes of < 0.01–0.21% energy [24], which is about 50% lower than the range 0.02–0.4% dietary energy from EPA and DHA in Japan [6]. Dietary advice to increase DHA from natural foods is advice to modify or increase the intakes of foods in the protein group, not fats and oils. The association of DHA with protein, and dissociation from total fat suggests that DHA metabolism and functions differ from the classical 14–18 carbon chain fatty acids that contribute over 95% of dietary fatty acids. The clear bioactivity of DHA at low intakes is more akin to a vitamin for which exogenous needs differ depending on life stage, background diet, genetic and other variables rather than to a dietary macronutrient. The association of DHA with animal tissues raises an intriguing question of why DHA should be involved in regulation of lipogenesis and glycolysis [21,22], and whether this may be part of a more complex regulatory network extending to amino acids.

3. Metabolic roles of DHA and EPA in the developing liver

The understanding about two decades ago that fatty acids regulate gene expression by binding to peroxisomal proliferator activated receptors (PPARs) opened the door to extensive research on the role of fatty acids and their metabolites in signaling pathways and metabolic regulation [41]. Since that time, about 50 ligand-activated transcription factors have been identified in humans, with the n − 3 fatty acids now known to target at least three hepatic transcription networks, these being PPAR-α, sterol regulatory element binding protein-1 (SREBP-1), and the carbohydrate regulatory element binding protein/Max-like factor X heterodimer (ChREBP/MLX) [22]. Activation of hepatic PPARα and transcription of its target genes, including genes involved in fatty acid oxidation, and inhibition of SREBP and ChREBP/MLX and their target genes, including genes involved in glycolysis and lipogenesis by n-3 fatty acids leads to increased fatty acid oxidation, and decreased glycolysis and fatty acid synthesis [21–23]. Although the importance of DHA when compared to EPA remains unclear, current understanding suggests DHA is the more potent suppressor of SREBP, but not of PPARα or ChREBP/MLX, than other n-3 or n-6 fatty acids [22,42]. Metabolic homeostasis and avoidance of cellular dysfunction, however, is more complex than co-ordination of glycolysis, lipogenesis and lipolysis, and this is particularly so in infancy when growth of lean tissues is important.

An intriguing aspect of infant physiology is the ability to sustain healthy growth and development with a milk diet that provides about 55% energy as fat, 37% as carbohydrate, and only 7–8% protein [27,34]. Before birth, fatty acids transferred across the placenta represent a minor portion of the fetal fuel supply, increasing from about 2% of the energy supply early in gestation to about 11% at term delivery [26]. The amount of DHA accumulated in the fetal and infant liver, however, depends on placental and then the milk (or milk alternate) supply of n-3 fatty acids, respectively [19,26,43]. A diet low in n-3 fatty acids, or with high 18:2n-6 reduces DHA, while dietary DHA increases the fetal and infant liver DHA and decreases the n-6 fatty acids. At birth, metabolic adaptation to frequent feeding with a high fat milk diet is crucial for survival This adaptation includes a rapid increase in hepatic mitochondrial and peroxisomal fatty acid oxidation, together with shifts in hepatic glycolysis, both of which are considered important to maintenance of glucose homeostasis in the infant [44–46]. Although muscle is the major site of fatty acid oxidation in adults [47], muscle mass and physical activity are low in the infant, suggesting the liver may play a central role in managing the high influx of milk-derived fatty acids. Regardless, little has as yet been done on the possible role of n-6 and n-3 fatty acids in metabolic regulation in the infant fed with a high fat milk diet, although it is known that fetal and neonatal liver DHA is highly dependent on the quality of the exogenous fatty acid supply [17–20,43]. This topic, however, has recently been gaining more attention due to ability of fish oils to reverse or protect against problems of intestinal failure associated liver disease in infants given intravenous lipids high in 18:2n-6 from soybean oil [48,49].

Glucose has key roles other than providing pyruvate and hence acetyl CoA for oxidation via the mitochondrial tricarboxylic acid (TCA) cycle, or for cytosolic fatty acid synthesis. These roles include the pentose phosphate pathway which contributes about 60% of NADPH in humans, and ribose-5-phosphate essential for RNA, DNA, ATP and other molecules (Fig. 1). The 3-phosphoglycerate pathway leads to synthesis of serine and glycine using glucose carbons and nitrogen from glutamate (Fig. 1), also generating the TCA cycle intermediate, α-ketoglutarate. Fatty acid β-oxidation generates acetyl CoA which must condense with oxaloacetate for oxidation via the TCA cycle, hence TCA cycle anapleurosis is essential to sustain fatty acid oxidation [50]. Glutamate is both the most abundant amino acid in milk [51], and also a key substrate for generation of TCA cycle intermediates [52,53]. Glycolysis can be inhibited at three steps; synthesis of glucose-6-phosphate via hexokinase, phosphofructokinase and