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Fatty acids and early human development

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Abstract

Fatty acids play central roles in growth and development through their roles in membrane lipids, as ligands for receptors and transcription factors that regulate gene expression, precursor for eicosanoids, in cellular communication, and through direct interactions with proteins. Adverse fatty acid supplies during fetal and child development alter the fatty acid composition of membrane phospholipids and storage triglycerides with the potential to disrupt cellular environments, and program structure and function. Maternal fatty acid nutrition during pregnancy and lactation determines the transfer of essential n-6 and n-3, and non-essential *trans* fatty acids *via* the placenta and through human milk. Poor maternal docosahexaenoic acid (DHA) status increases risk of inadequate DHA to support brain and retinal development, delaying or limiting neural and visual system development. The implications of recent changes in the dietary fatty acids on maternal to infant fatty acid transfer, including the composition of human milk has been insufficiently studied.

1. Introduction

Dietary fat has long been considered from the perspective of a concentrated source of energy, providing metabolic efficiency to support adipose tissue growth and spare protein for accretion of lean tissue during development. Early studies established that the requirement for essential n-6 fatty acids is only 1–2% of dietary energy, thus the abundant n-6 fatty acids in usual diets raised little reason to question the importance of human milk fatty acids as modifiable nutrients important in infant development. The predominance of glucose as a metabolic fuel for the fetus, together with the hypothesis for selective transfer of certain n-6 and n-3 fatty acids across the placenta similarly infers that dietary fat composition during pregnancy is of little consequence to fetal development. However, dietary fatty acid intakes during pregnancy and lactation clearly influence maternal-to-infant transfer of fatty acids before and after birth with both beneficial and adverse effects on infant development. This paper focuses on recent research to show that maternal dietary fatty acids have important implications for human development, with a specific focus on the central nervous system.

2. Dietary fatty acids: metabolism and dietary intakes

Although fatty acids are important as sources of metabolic and storage energy, the role of n-6 and n-3 fatty acids as components of membrane phospholipids, precursors for eicosanoids, and as ligands for membrane receptors and transcription factors that regulate gene expression is of particular importance in human development [1–5].

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Whereas *de novo* lipogenesis leads to synthesis of saturated and monounsaturated fatty acids, mammalian cells lack Δ-12 and Δ-15 desaturase enzymes and, therefore, depend on diet for the n-6 and n-3 polyunsaturated fatty acids [1,2]. The major dietary n-6 and n-3 fatty acids are the 18 carbon n-6 linoleic acid (LA, 18:2n-6) and n-3 α-linolenic acid (ALA, 18:3n-3), which are obtained predominately from unsaturated vegetable oils. Animals, including humans, but not plants, can desaturate and elongate LA to arachidonic acid (ARA, 20:4n-6) and ALA to eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3) [1,2]. Humans, therefore, consume ARA, EPA and DHA in animal tissues, with fatty fish being the richest source of EPA and DHA. Humans have a low capacity for *de novo* lipogenesis, which together with the inability to form n-6 and n-3 fatty acids means that the dietary fatty acid supply is important to the fatty acids incorporated into tissue lipids, including phospholipids. Phospholipids contribute to the structural matrix of all cell membranes and provide a dynamic reservoir of n-6 and n-3 fatty acids which influence membrane lipid-protein interactions, and which are continuously turned-over, facilitating inter- and intra-cellular signaling and generating ARA, EPA and DHA for synthesis of eicosanoids and resolvins, and ligands for transcription factors that regulate gene expression [2–6]. As a result, diet-induced changes in ARA, EPA and DHA have the potential to modulate cellular functions on many levels.

DHA is enriched in brain grey matter and retina phospholipids, and represents 3–5% of the dry weight of these tissues [1,2]. Dietary deficiency of n-3 fatty acids decreases brain and retina DHA, impairs neurogenesis, alters gene expression and neurotransmitter, including dopamine and serotonin metabolism, and decreases the kinetics of the visual photocycle [3]. ARA is found in phospholipids throughout the body and is important in growth, and as a precursor for eicosanoids pivotal in numerous physiological, including immune and inflammatory pathways [1–6]. Eicosanoid metabolism is complex, and although early work considered eicosanoids derived from EPA as less and those derived from ARA as more pro-inflammatory, recent advances have shown that ARA-derived lipoxins are important in the resolution of inflammation [7]. Long chain n-3 fatty acids lower ARA by inhibiting the conversion of LA to ARA and competing for acylation into phospholipids; thus, an appropriate balance of ARA, EPA and DHA is important to support normal growth, immune function and CNS development.

Over the last century, an increase in LA-rich vegetable oils and hydrogenated oils high in *trans* fatty acids have resulted in marked changes in fatty acid intakes [7]. Average intakes of LA and ALA in many western nations are 5–7% and 0.5–1.0% dietary energy, equivalent to 11–16 g and 1.1–2.2 g/d in a 2000 kcal diet, respectively, giving a LA/ALA ratio of 10:1 or higher, compared to 3:1 at the beginning of the last century [7,8]. Only 1–2% dietary energy from LA is needed to support growth and achieve high tissue levels of ARA, and higher LA intakes increase circulating and tissue LA and decrease EPA, resulting in an increase in the ARA to EPA balance [9,10]. *Trans* fatty acids are associated with an increased risk of cardiovascular diseases and systemic inflammatory mediators, and are incorporated directly, or after further metabolism into tissues [11–13]. Most *trans* fatty acids are now consumed in bakery and convenience foods, rather than table margarines [14]. Average intakes of ARA, EPA and DHA in many westernized countries are 0.08–0.12 g/d [8,15], but individual intakes vary widely. Humans, including newborn infants convert less than 1% of dietary ALA to DHA [16–18]. Increasing dietary ALA has little effect in increasing maternal to infant DHA transfer either before birth, or through increasing DHA secretion in milk [19,20]. Similarly, increasing the intake of ALA in infants, as in adults, has little effect in increasing on circulating levels of DHA [10,21]. The importance of DHA in the CNS together with the low conversion of ALA to DHA thus raises the question of whether a dietary source of DHA is important for optimal human neural and visual function.

3. Maternal dietary fatty acids: implications for placental fatty acid transfer and the secretion of fatty acids in human milk

Placental transfer of fatty acids involves a multi-step process of uptake and translocation facilitated by fatty acid binding proteins; proteins that favour n-6 and n-3 fatty acids over non-essential fatty acids, and ARA and DHA over LA or ALA have been identified [22]. Fatty acids released by the placenta are transported to the fetal liver, esterified and secreted in lipoproteins, of which HDL is prominent. Fetal lipoprotein phospholipids, triglycerides and cholesteryl esters have higher ARA and DHA, and lower LA than in infants after birth, or in maternal plasma [22,23]. However, epidemiological and intervention studies have shown that higher maternal intakes of *trans*, and n-6 and n-3 fatty acids, including DHA increase maternal to fetal transfer of the respective fatty acid [11,22–25]. Circulating levels of *trans* fatty acids in newborn infants are inversely associated with ARA and DHA, and birth weight, which could be explained by *trans* fatty acid interference with n-6 and n-3 fatty acid metabolism, or by poor dietary fatty acid quality in women with diets high in *trans* fatty acids [22,23]. Plasma phospholipid DHA levels vary from 4 to 12% among newborn term infants [23], raising the question of whether low fetal DHA status during gestation leads to deficits in infant CNS development.

Human brain growth is at peak velocity during the last three months of gestation and first few months after birth, leading to the concept that the third trimester fetus and newborn infant are particularly vulnerable to developmental deficits if DHA is limiting [9,26]. The critical role of DHA in neurogenesis, however, suggests that adverse affects of inadequate DHA in early gestation will be more to severe and more difficult to overcome than deficiencies occurring later on [3]. On the other hand, the growth of dendritic arbors and peak formation of synapses, which are enriched in DHA, extends from about 34 wk gestation through 24 mth after birth, during which time new connections form at rates up to almost 40,000 synapses/s [27]. The accumulation of DHA in the human forebrain also continues linearly for at least 24 mth after birth [28]. In autopsy analysis, 52 of 67 mg/d of n-3 fatty acids, of which 90% was DHA, accumulated by the third trimester fetus was in adipose tissues [26]. Thus, later gestation involves accumulation of a large adipose tissue DHA reserve. Infants born with higher blood levels of DHA, as well as ARA maintain this advantage for several weeks [29,30], suggesting that fatty acids accumulated in fetal adipose tissue are released for uptake by other organs in the postnatal