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Review

Transport of fatty acids across the human placenta: A review

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ABSTRACT

Essential fatty acids and their long chain polyunsaturated fatty acid derivatives (20 C) such as docosahexaenoic and arachidonic acids are critical for proper fetal growth and development. Dietary intake as well as metabolism of these fatty acids, and their subsequent transfer from the mother to the fetus are therefore important requisites for developing fetus. The placenta is the key organ through which nutrients such as these fatty acids flow from the mother to the fetus. Cellular uptake and translocation of long chain fatty acids (LCFAs) in different tissues is achieved by a concert of co-existing mechanism. Although LCFA can enter the cell via passive diffusion, emerging reports indicate that LCFA uptake is tightly regulated by several plasma membrane-located transport/binding proteins such as fatty acid translocase (FAT/CD36), plasma membrane fatty acid binding protein (FABPpm), fatty acid transport protein (FATP) and intracellular FABPs in several tissues including human placenta. Fatty acid activated transcription factors (PPARs, LXR, RXR, and SREBP-1) have been demonstrated to regulate these fatty acid transport/binding proteins, and placental functions. Maternal fatty acids therefore may regulate their own placental transport as well as placental function via several fatty acid-activated transcription factors. This review summarizes recent developments on placental fatty acid transport and metabolisms, and the regulatory roles of these proteins in these processes.

Contents

Abbreviations: ACSBG, acylCoA syntheatse bubblegum; ADRP, adipose differentiation-related protein; ARA, arachidonic acid; ALA, α linolenic acid; Cyclooxygenase, COX; $cPLA_2$, cytosolic phospholipase A_2; DHA, docosahexaneoic acid; EL, endothelial lipase; EFA, essential fatty acids; FABPs, fatty acid binding proteins; FABPpm, plasma membrane fatty acid-binding protein, FATP, fatty acid transporter protein, FAT, fatty acid translocase, hCG, human chorinnic gonadotropin; HETE, hydroxy-5Z,11Z,13E-eicosatetraenoic acid ; HODE, hydroxy-octadedienoic acid; IUGR, intrauterine growth retardation; IDDM, insulin dependent diabetes mellitus; LA, linoleic acid; LCFA, long chain fatty acids; LDL, low density lipoproteins; LPL, lipoprotein lipase; LCPUFA, long chain polyunsaturated fatty acids; LXR, liver X receptor; mAspAT, mitochondrial aspartate aminotransferase; OA, oleic acid; PA, palmitic acid, PPAR, peroxisome proliferator-activated nuclear receptors; PG, prostaglandins, RXR, retinoid X receptor; SREBP-1, sterol regulatory element binding prtein-1; VLDL, very low density lipoproteins.

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1. Introduction

Essential fatty acids (EFA) and their long-chain polyunsaturated fatty acids (LCPUFA) are of critical importance in fetal growth and development [1–4]. These fatty acids are the precursors of eicosanoids and are essential constituents of the membrane lipids that maintain cellular and organelle integrity and important intracellular mediators of gene expression [5–9]. Because of these fundamental roles of EFA and LCPUFA, the maternal, fetal, and neonatal EFA/LCPUFA status is an important determinant of health and disease in infancy and later life. The deposit of these LCPUFA to the fetus is rapid during growth, and it is suggested that a failure to accomplish a specific component of brain growth because of inadequacy these fatty acids. In fact, fetal brain and retina are very rich in LCPUFA specially, arachidonic acid, 20:4n-6 (ARA) and docosahexaenoic acid, 22:6n-3 (DHA) [10–12]. Evidence from various studies suggests learning ability may be permanently impaired if there is a reduction in the accumulation of sufficient DHA during intrauterine life [13,14]. The premature babies, in particular, born during the last trimester of pregnancy have been shown to have low levels of DHA in the blood; this has been correlated with their abnormal eye and brain functions as measured by electroretinogram, cortical visual-evoked potential, and behavioral testing of visual acuity [9,14]. The critical importance of EFA/LCPUFA in feto-placental unit demands an efficient uptake system for these fatty acids and their metabolism.

Several plasma membrane fatty acid binding/transport proteins (FABPpm, FATP, and FAT) and intracellular fatty acid binding proteins (FABPs) have been suggested to be involved in cellular uptake and transport of fatty acids in human placenta [1,15]. In addition, involvement of several nuclear transcription factors (PPARs, LXR, RXR, and SREBP-1) in the expression of genes responsible for fatty acids uptake, placental trophoblast differentiation and human chorinnic gonadotropin (hCG) production indicating regulatory roles of fatty acid-activated transcriptions factors in placenta biology [16–21]. Maternal fatty acids thus may affect their placental transport as well as placental biology. Therefore, elucidating the pathways of placental fatty acid transport and metabolism, and the regulatory processes governing these pathways is critical for advancing our understanding the relationships between maternal fatty acid metabolism and the placental supply of EFA/LCPUFAs to the developing fetus and the potential implications on pregnancy and fetal outcome [20]. In this review, I would summarize recent development in the biochemical processes involved in placental fatty acid transfer to the fetus.

2. Maternal metabolism and supply of essential fatty acids (EFA) and LCPUFA to the fetus

Linoleic acid, 18:2n-6 (LA), and α-linolenic acid, 18:3n-3 (ALA) are the two main dietary EFA that are readily available from the dietary sources such as vegetable oils, but their LCPUFA derivatives (ARA, EPA, DHA) can be consumed in foods of animal origin. Dietary LA and ALA must be converted in the body to their further metabolites, LCPUFA to exert the full range of biologic actions. Therefore, maternal EFA metabolism is crucial for fetal growth and development, as the fetus depends on the maternal supply of LCPUFA such as ARA and DHA. ARA is a precursor for bioactive eicosanoids and leukotrienes. The different prostaglandin and leukotrienes, affect numerous immune inflammatory responses, including fetal thymic growth, whereas both DHA and ARA are an important structural component of the nervous system. A deficiency of these important fatty acids in the critical times of embryological organogenesis may be devastating, particularly in neurological 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, an integral component of neuronal membrane is in an inadequate supply. Such an important role of DHA rests on its participation in maintaining membrane fluidity, impulse propagation, synaptic transmission, and its function as a cytosolic signal transducing factor for various gene expression during the critical period of brain development [22,23]. 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 [24]. Infants born with higher blood levels of DHA, as well as ARA maintain this advantage for several weeks [25,26], as the fatty acids accumulated in fetal adipose tissue are readily available for release and uptake by other organs in the postnatal period. The breast fed infant may have an additional advantage – its mother's milk, rich and readily available source of customized food components. Optimal maternal to fetal DHA and ARA transfer in gestation is, therefore, likely to have benefits both before birth and extending into the postnatal period and thus, mother's physiological adaptation towards this feto-maternal cooperation must be remarkably coordinated. During early pregnancy, LCPUFA derived from the diet are stored in maternal adipose tissue. During late pregnancy, enhanced lipid catabolism as a consequence of the insulin-resistant condition, in part due to hyperestrogenism, causes the development of maternal hyperlipidemia, which plays a key role in the availability of LCPUFA to the fetus. Maternal body fat accumulation during early pregnancy allows the accumulation of an important store of LCPUFA derived from both the maternal diet and maternal metabolism. The importance of DHA during pregnancy in fetal development and its postnatal spill-over effect has been studied, by examining the relationships between maternal DHA intake during gestation and lactation on cognitive functioning in later childhood [14,27]. Although interventional studies to inquire into the importance of DHA in pregnancy and fetal development, are complicated by different variables, such as, food habits, placental functions, and transit to fetal circulation etc., several epidemiological and interventional studies do suggest that higher maternal intakes of n-6 and n-3 fatty acids, including DHA increase maternal to fetal transfer of the respective fatty acid.

In the large ALSPAC cohort study the frequency of seafood consumption during pregnancy in 11,875 women, a marker of dietary n-3 LCPUFA intake, was compared to the developmental, behavioral and cognitive outcomes of the children up to school age [28]. The authors found a significantly increased risk for children of mothers who consumed less than 340 g fish/week to be in the lowest quartile for verbal intelligence at the age of 8 years. Low maternal fish intake was also associated with sub-optimal outcomes in fine motor skills and social developmental scores. In Europe the average dietary supply of LCPUFA and especially of DHA is rather low [29]. Large observational studies have shown that children of women with low fish intakes during pregnancy are at increased risk of poor cognitive and behavioural outcome [28,30]. Similarly, low blood levels of DHA in infants at birth or during breast-feeding are associated with lower visual and neural maturation in infancy, and later childhood [31–34]. Multivariate analyses showed that infant gender and maternal DHA supplementation were significantly related to visual acuity at 60d age; infants in the placebo group were more likely to have a visual acuity below the mean, by gender, than infants in the DHA supplemented group. Others have shown that infants with a higher DHA status at birth have more mature electroencephalography patterns at 2d of age, higher visual functional maturation in infancy, and less distraction and better attention in the second year of life [32–34].