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Fatty Acid Transporting Proteins: Roles in Brain Development, Aging, and Stroke

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Abstract

Polyunsaturated fatty acids are required for the brain development and significantly impact aging and stroke. Due to the hydrophobicity of fatty acids, fatty acids transportation related proteins that include fatty acid binding proteins (FABPs), long chain acyl-coA synthase (ACS), fatty acid transportation proteins (FATPs), fatty acid translocase (FAT/CD36) and newly reported major facilitator superfamily domain-containing protein (Mfsd2a) play critical roles in the uptake of various fatty acids, especially polyunsaturated fatty acids. They are not only involved in neurodevelopment, but also have great impact on neurological disease, such as aging related dementia and stroke.

Introduction

Aging is a complex process that is accompanied by damage to cellular components, including proteins and critical lipids susceptible to accumulation of damage as a result of oxidation, nitrosylation or inflammation, among other insults. The lack of n-3 polyunsaturated fatty acids (n-3 PUFAs) in the Western diet through lifetime may gradually induce a chronic DHA deficit of lipid membranes in the brain. This may contribute to a chronic pro-inflammatory state in the brain, which is characteristic for brain aging in later life associated with dementia [1]. We and others have suggested that sufficient intake of n-3 PUFAs protects the brain against cerebral ischemia and improves neurological outcomes. In addition to intake via the diet, the cellular uptake of fatty acids is greatly dependent on

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specialized proteins required for fatty acids transportation. Herein, we will summarize the metabolism of polyunsaturated fatty acid in brain and the function of proteins critical for fatty acids transportation during neurodevelopmental and aging processes.

Metabolism of PUFAs in mammals

Polyunsaturated fatty acids (PUFAs) contain more than one double bond structurally. According to the localization of the first double bond from the methyl terminal end (ω carbon terminal), PUFAs are classified into two classes: n-3 families, which include α-linolenic acid (ALA, C18:3), eicosapentaenoic acid (EPA, C20:5), docosapentaenoic acid (DPA C22:5n-3) and docosahexaenoic acid (DHA, C22:6), and n-6 polyunsaturated fatty acids, such as linoleic acid (LA, C18:2), arachidonic acid (AA C20:4) and docosapentaenoic acid (DPA C22:5n-6). PUFAs cannot be synthesized *de novo* in vertebrate tissue because of the deficiency of Δ-12 and Δ-15 desaturases, which are enzymes necessary to produce the so-called essential fatty acids, ALA and LA [2]. With the deficiency in the ability to synthesize these lipids, mammalians primarily depend on a dietary source for polyunsaturated fatty acids, especially ALA and LA. After dietary consumption of ALA and LA, most mammalian tissue can construct 20-carbon unsaturated fatty acids (like EPA and AA) and 22-carbon unsaturated fatty acids (like DHA and DPA) from the ALA and LA by elongation and desaturation, which occurs in the endoplasmic reticulum, together with final β-oxidation taking place in the peroxisome (Figure 1). The liver is considered to be the primary site that produces DHA, EPA and AA from their dietary precursors, and then releases them to the blood flow to supply other tissues. Similar with other fatty acids, adipose tissue is the major storage site for PUFAs, which can then be released to plasma during times of systemic deficiency, including fasting.

Impact of diet and aging on cerebral PUFAs content

Dietary conditions significantly influence the content of long chain PUFAs–especially DHA–in the central nervous system. Long-term dietary restriction of n-3 PUFAs in rodents and cats upregulates the expression and activity of the enzymes elongase and desaturase, critical for the conversion of DHA from ALA, but that this response is primarily in liver rather than in brain [3, 4]. Despite of the elevation of DHA synthesis in the liver, the DHA levels in the liver remain lower than that in brain tissue, suggesting that the DHA synthesized in the liver is transported to the brain to maintain the cerebral DHA levels [5–7]. Prolonged deprivation of n-3 PUFAs significantly reduces its total concentration in brain, particularly in oligodendrocytes, myelin, synapsomes and astrocytes. However, the DHA level in neurons is only slightly affected, indicating the preferential supply or maintenance of PUFAs to or in neurons. Interesting, chronic dietary DHA deficiency in rats deceases n-3 PUFAs in the liver and plasma, but re-supplementation effectively restored levels of DHA within 2 weeks. However, the levels of cerebral DHA after re-supplementation do not return to normal until 8 weeks later, indicating the accumulation of DHA is slower in brain compared to other organs [8] (Figure 2).

As n-3 and n-6 shares the same elongation/desaturation enzymes for their synthesis, chronic deprivation of n-6 PUFAs in rats decreases the loss of arachidonic acid and increases DHA

metabolism to promote neuroprotection and alter neurotransmission [9–11], while deficiency in n-3 PUFAs induces the turnover of n-6 long chain unsaturated fatty acids [12]. Their metabolic cascades are altered reciprocally by the change of dietary PUFAs [11, 13, 14]. Therefore, diminishment of brain DHA (C22:6n-3) can lead to the increase of DPA (C22:5n-6), with one fewer double bond at the terminal methyl end of the chain [15, 16]. The replacement of DHA (n-3) with DPA (n-6) may alter the properties of neural membranes and the function of integral receptor proteins [17]. n-3 PUFAs compete with n-6 fatty acids for elongation/desaturation enzymes that catalyze them; thus, dietary supplementation of n-3 PUFAs significantly increases the concentration of DHA, and leads to a decrease in n-6 derived PUFAs such as AA in the cerebral cortex of rodents [18–20]. This shift in fatty acid make up can contribute to development of a neuroprotective state.

The influence of aging on the cerebral polyunsaturated fatty acid content is less understood. In human, DHA and AA are decreased in the membranes of human orbitofrontal cortex in the elderly population [21]. Dietary consumption of fish is correlated with larger volume of gray matter, better white matter grade detected by MRI, lower prevalence of subclinical infarct [22, 23]. Several studies have suggested that the aging brain (22 month-old) is prone to lose DHA in rodents [24, 25]. The specific DHA deficiency in aged brain may result from an age-related reduction in the activity of the enzymes specifically regulating DHA synthesis in liver, as well as its uptake and assembly into brain phospholipids [26–28]. Despite the age-related loss of DHA observed in rodents, dietary supplementation of DHA in aged rats can prevent such losses [29, 30].

Uptake of PUFAs in brain

Synthesis of DHA and AA from their precursors can occur in vertebrate tissue, but is extremely limited, particularly in brain. Cerebral and cerebellar neurons are capable only conducting fatty acids elongation, but lack the capacity for desaturation required for the complete production of DHA and AA [31]. Endothelial cells in the brain microvasculature provide a substantial amount of elongation and desaturation products to the brain parenchyma. While the endothelial cells predominantly produce AA (n-6) and EPA (n-3) from their 18-carbon precursors, astrocytes subsequently complete the conversion to the 22-carbon forms DPA (n-6) and DHA (n-3), respectively. Astrocytes are thought to be a major source for DHA and AA conversion from precursor PUFAs in the brain, but hippocampal neurons may also possess the ability to convert low amounts of precursor PUFAs into DHA and AA [32]. DHA and AA produced by astrocytes can be released and rapidly taken up by neurons and incorporated into their plasma membranes [31, 33, 34]. The free precursors of DHA and AA undergo rapid β-oxidized upon their entry into brain [6, 35, 36] and are not stable. Therefore, the uptake of preformed DHA and AA plays a critical role in the cerebral accumulation and maintenance of PUFAs content in adult brain [37].

Astrocytes and endothelial cells, two major components of the blood brain barrier, are the major contributors to the transportation of PUFAs from the circulation to brain. The uptake of PUFAs into brain may occur by distinct or overlapping mechanisms, including passive diffusion a saturable transport process. PUFAs are carried through the plasma by albumin and circulating lipoproteins, and, after release from these proteins, PUFAs bind to the

luminal surface of endothelial cells, integrate into the external phospholipid bilayers as uncharged molecules, and then translocate to the inner leaflet of phospholipid bilayers by flip-flop. At the inner surface of endothelial cell membranes, a small portion is delivered into the subcellular compartments for further metabolism, while most of the fatty acids diffuse into the cytosol with or without the aid of membrane proteins [38, 39]. Subsequently, these fatty acids repeat the flip-flop process and go through the abluminal membrane of endothelia with the aid of transportation proteins. ALA and LA are transported to astrocytes for DHA and AA synthesis to be provided to neurons. These PUFAs are finally absorbed from circulation to the neurons, and incorporated into their membrane structures. There are four classes of lipid transportation proteins involved in lipid synthesis and transportation in adult brain, including fatty acid translocase (FAT/CD36), caveolin-1, fatty acid binding proteins (FABPs) long chain acyl-coA synthase (ACS) and fatty acid transportation proteins (FATPs). Additionally, Mfsd2a is newly identified as a DHA transporter in brain (Figure 3). We will first summarize the roles of these lipid transportation related proteins in LC-PUFAs accumulation in fetus and adult brain, and then focus on their functions in neurological diseases.

1. Fatty acid-binding proteins (FABPs)

Fatty acid-binding proteins (FABPs) are divided into two groups: plasma membrane associated proteins (FABPpm) and cytoplasmic proteins (FABPc) according to their subcellular localization. FABPpm, a single polypeptide of approximately 40 kDa, is anchored at the outer surface of the cell membrane and functions with specific affinity to long-chain fatty acids [40–42]. FABPpm facilitates the dissociation of fatty acids from albumin, which leads to the accumulation of fatty acids in the outer leaflet of phospholipid bilayer and their subsequent flip-flop into the inner leaflet [41, 43]. Cytoplasmic FABPs belong to a superfamily of lipid-binding proteins with low molecular mass (14–15 kDa). Thus far, nine different FABPc molecules have been identified, which have been named according to the tissue of their dominant expression or first isolation. FABPs bind only one fatty acid molecule at a time, with the exception of the liver type, which has the capacity to bind to two molecules at the same time. Among the nine members, three of them have been detected in central nervous system of rodents, specifically the epidermal-type (E-FABP, or FABP5), brain-type (B-FABP, or FABP7), and heart-type (H-FABP, or FABP3) [44, 45]. Each of these FABPs display a specific temporal and spatial expression pattern.

E-FABP mRNA is mainly distributed in the ventricular germinal zone to cortical plates at the embryonic stage, whereas in the adult, the expression is evident in both neurons and glia in each brain region. E-FABP preferentially combined with saturated fatty acids and was detected in the hippocampal radial glia and in the neurons of the cerebral cortex [46, 47]. B-FABP mRNA, which was first identified in neuroepithelial precursor cells of developing brain, is abundantly expressed in developing radial glial cells in both the ventricular and subventricular zones, but is expressed at a much lower level in mature rodents. Within the brain, expression is detectable in the olfactory nerve fiber layers, hippocampal dentate gyrus, and the cerebellar Purkinje cell layer, all areas where there is prominent neurogenesis. Consistent with its mRNA distribution, B-FABP protein is expressed in astrocytes of white matter radial glial cells and Bergmann's glial cells throughout development. B-FABP tends

to bind to n-3 PUFAs, and displays a higher affinity for DHA, suggesting a significant role in maintaining DHA concentrations in brain during cerebral development [48]. Neurogenesis in B-FABP-null mice is attenuated, and supports the role of DHA uptake in brain development [49]. In contrast to E-FABP and B-FABP, H-FABP expression becomes evident beginning in the postnatal rat brain and gradually increases, leading to high expression in neurons of the cortical layers, hippocampus and dentate gyrus in adult brains. H-FABP displays a preferential affinity for the n-6 PUFA family, and ablation of H-FABP decreases the uptake and the concentration of arachidonic acid in brain [50]. Briefly, differential preferences for the binding of fatty acid types results in a selection for specific cellular uptake of fatty acids based on FABP-specific expression, whereas the phase-specific expression of different fatty acids binding protein indicates the pivotal role of PUFAs in development and the importance of PUFAs supply to the brain in the neurodevelopmental process.

Fatty acid-binding proteins prevent the oxidation of unsaturated fatty acids, regulate the cellular uptake of fatty acids and subsequent metabolism, and promote the storage of fatty acids thereby accelerating their subsequent passive diffusion across the plasma membrane. FABPs also facilitate the transportation of fatty acids to nuclear receptors such as PPARs, where they demonstrate gene regulatory activities [51].

2. Fatty acid transport proteins (FATPs)

The FATPs are a group of membrane proteins that facilitate the import of long-chain fatty acids. The two highly conserved domains are related to hydrolysis and ATP-binding; the latter appears to be essential for FA transport activity [52]. Once the PUFAs are within the cell, FATPs act via fatty acyl-CoA synthetase (ACS) activity to promote the activation of intracellular fatty acids and prevent the efflux of PUFAs [53, 54]. The long-chain fatty acyl-CoA derivatives act not only as substrates but also intermediates in multiple intracellular functions.

Among the six characterized members of the FATP family, FATP1 is the predominant FATP expressed in the central nervous system [55]. The FATP1 gene is highly conserved in biology from bacteria to mammals. Several factors regulating FATP1 gene expression have been described in rodents and cultured cells, including upregulation by peroxisome proliferator-activated receptors (PPAR) [56], selective retinoid X receptor (RXR) ligands [57] and fasting [58], and downregulation by insulin [59]. With a very short segment of N-terminus incorporation at the extracellular side, FATP1 is predominantly oriented toward the cytoplasm, along with two membrane loops within the inner leaflet, and a cytosolic carboxyl terminus. The conserved ATP-binding motif is localized to non-membrane-associated residues in cytosolic side. This motif is common to acyl-CoA synthetases (long chain and very long chain) which is required for the production of the acyl-adenylate reaction intermediate [60]. Mutation of serine 250 to alanine within this ATP-binding motif results in decreased fatty acid transport activity and enzyme catalytic inactivation [52, 53]. The second conserved motif is a fatty acids binding domain, which distinguishes very long chain acyl-CoA sequences from long chain acyl-CoA sequences. Interestingly, it is also necessary for catalytic activity [53]. Overexpression of FATP1 in 3T3-L1 cells results in the accreted

internalization of palmitic acid (PA), oleic acid (OA) and AA without any specific preference for these fatty acids [61]. Knockdown of FATP1 in human brain microvessel endothelial cells (HBMEC) abrogated the movement of OA and PA but not LA from apical to basolateral medium, indicating that the degree of unsaturation may not be important for fatty acids transport by FATP1 in HBMEC [62].

FATP4 is also highly expressed in human and murine brain, and possesses acyl-CoA activity [55, 63, 64]. Overexpression of FATP4 in 293 cells exerts little effects on ARA internalization [65]. In HBMEC, knockdown of FATP4 significantly decreased the movement of linoleic acid, while slightly increased that of oleic acid from the apical to the basolateral medium, suggesting that other fatty acid transport proteins participate to compensate FATP4 deficiency [62].

3. Fatty acid tranlocase (FAT/CD36)

FAT/CD36 was first cloned in adipocytes as a highly glycosylated (10 predicted N-linked glycosylated sites) polypeptide chain with molecular weight of 88 kDa. Due to the high sequence similarity (85%) between FAT cloned from rat and the human leukocyte differentiation antigen CD36, FAT was also named as CD36. FAT/CD36 is proposed to contain two trans-membrane domains located at either ends of the molecule with extreme short C- and N-terminal intracytoplasmic domains and a large, multiply N-glycosylated extracellular loop [66]. It anchors in lipid rafts on the surface of a wide variety of cells, such as myocytes, hepatocytes, adipocytes, and endothelial cells in the microvasculature. The fatty acid binding site may be located in its extracellular segment between residues 127 and 279. FAT/CD36 binds long-chain fatty acids with high affinities and functions as a major facilitator of fatty acid release from albumin and subsequent uptake in muscle and adipose tissues, which is influenced by the presence of caveolin-1 and lipid rafts [67–69]. Besides free fatty acids, FAT also has affinity for collagen, thrombospondin, anionic phospholipids and oxidized low-density lipoprotein (oxLDL) and demonstrates multiple functions [66].

In brain tissue, FAT/CD36 is distributed on microvascular endothelial cells and microglia/macrophage, indicating its potential role in maintaining the concentration of PUFAs in brain and involvement in regulating inflammation, respectively [70, 71]. FAT/CD36 is also expressed in human placenta including the placental membranes, microvillous and basal membranes to act in concert with FABPpm and FATP in LC-PUFAs transportation and uptake during development. Overexpression of FAT/CD36 results in an elevated rate of fatty acid uptake, whereas FAT/CD36 deficit leads to reduced fatty acid uptake. In HBMEC, knockdown of CD36 abrogates transport of short-chain, medium-chain and long-chain saturated and unsaturated fatty acids, as well as very-long chain fatty acids, which support its detrimental role in transport of fatty acids across HBMEC [62]. Knockout of CD36 in mice leads to a decrease in monounsaturated fatty acids in several brain phospholipid fractions, with no significant differences in AA or DHA concentrations among different brain regions [72]. However, CD36 null mice present with a deficit in cognitive function, indicating that CD36 have impact on memory ability unrelated with large changes in brain PUFAs content [73, 74].

4. Mfsd2a

Mfsd2a, a novel mammalian *major facilitator superfamily domain-containing protein*, is a newly reported DHA transporter that is expressed in brain [75]. First identified by Martin in 2008 [76], two isoforms, Mfsd2a and Mfsd2b, have been identified thus far. Most of intron/exon junctions between the two genes are conserved, which suggests that they may be derived from the same ancestor, and they share the structural element of 12 transmembrane α-helical domain with a 29% similarity to the bacterial Na+/melibiose symporters [76]. In humans, Mfsd2a has been characterized as the target of syncytin-2, which is critical for cytotrophoblast fusion and placenta development [77–79]. Mfsd2a localizes to the endoplasmic reticulum and is robustly increased in liver and brown adipose tissue during fasting by stimulating β-adrenergic receptor signaling pathway [80]. Distinct from the peripheral inducible expression, Mfsd2a is constitutively expressed in brain. As a DHA transporter, Mfsd2a specifically transports common plasma lysophosphatidylcholines (LPCs) by carrying long-chain fatty acids such LPC oleate and LPC palmitate, rather than LPCs with less than a 14-carbon acyl chain. Mfsd2a is required for the brain uptake of DHA [75, 81]. Mutation of the Mfsd2a serine 339 to leucine has no impact on protein or cell surface expression, but greatly reduces its transportation activity, leading to a progressive microcephaly syndrome [82]. Genetic knockout of Mfsd2a in mice increases energy expenditure and ataxic movements, indicating a role in regulating lipid metabolism, growth and development, and motor functions [80, 81]. Ablation of Mfsd2a leads to increased leakiness of the blood brain barrier from embryonic stages through adulthood, without obvious tight-junction deficits. Consistently, Mfsd2a expression in endothelium is regulated by pericytes to maintain the blood brain barrier integrity, suggesting its functional role in the development of the blood brain barrier [83]. The involvement of Mfsd2a in neurological diseases, particularly those involving the integrity of the blood brain barrier, deserves further investigation.

Given the extensive presence of fatty acid transportation proteins and fatty acid-binding proteins in the brain, it is possible that they are critically involved in the uptake and enrichment of PUFAs into brain. Endothelium and astrocytes, constituents of the blood brain barrier, provide PUFAs to neurons and block the egress of PUFAs from brain tissue. In spite of extensive knowledge on fatty acids transportation-related proteins, the detailed mechanisms by which brain tissue concentrates PUFAs are not well understood; for example, it is still unclear to what extent simple diffusion versus protein-mediated transportation contribute to the total rate of PUFAs uptake. These topics deserve further investigation in the future.

Accumulation of PUFAs in the fetus

The state of fetal PUFAs is hypothesized to be a critical determinant of health and disease extending into later life. Since the capacity for conversion from precursor PUFAs to DHA and AA is negligible in the fetus, maternally derived essential fatty acids (EFAs) are required for fetal brain development. The concentration of DHA and AA in cord plasma is double maternal levels, indicating that LC-PUFAs is needed by the fetus [84]. In human, the fetal and infant brain DHA is more prone to be affected by diet than AA content, indicating

the more effective endogenous regulation of AA synthesis [85]. Subsequent esterification of DHA peaked after being absorbed, with 60% DHA incorporated into triacylglycerol and 37% in phospholipid fractions. Contrary to DHA, 60% AA esterified into phospholipids fraction and <35% into triacylglycerol fraction. Although it is still unknown about how and in what form DHA is transported into the fetal circulation from the placenta, DHA integration into triacylglycerols may be helpful for DHA transportation to the fetal circulation.

The placenta may exert critical control on the preferential intake of LC-PUFAs and subsequent transportation from the mother to the fetus. The directional materno-fetal translocation of PUFAs cannot be completely explained by simple diffusion and partition mechanisms. Unregulated diffusion is quantitively less critical than protein-mediated fatty acids transportation across the membranes in the fetus [86]. The identification of fatty acids transportation related proteins (as discussed above, including FABPpm, FABP, FAT/CD36, and FATP) in placenta further implies the critical function of a protein-mediated fatty acids translocation pathway in directional materno-fetal translocation of PUFAs [84, 87, 88].

1. Placenta specific plasma fatty acid-binding protein (FABPpm)

Plasma fatty acid-binding protein (FABPpm), a member of FABP family, is detectable in both human and sheep placenta [88, 89]. However, this placenta-specific FABPpm (p-FABPpm), with a molecular mass of 40kDa, is different from the previously described FABPpm on the basis of its pI value, amino acid composition and fatty acid binding activity [89]. p-FABPpm resides entirely in the microvillus membranes on the side facing maternal circulation and has preferential affinity to EFAs/LC-PUFAs, especially DHA and AA, compared to unessential fatty acids [90, 91]. Uptake of LC-PUFAs and EFAs is blocked by anti-FABPpm, with the order of inhibition DHA>ARA≫ALA>LA≫OA, suggesting the potential role of p-FABPpm in the preferential uptake of LC-PUFAs from mother to fetus [92, 93].

Besides p-FABPpm, there are two cytosolic isoforms of FABPs (heart isoform and liver isoform) identified in both human and rat placenta [94, 95]. In rat mid to late gestational placental regions, H-FABP is predominantly expressed in the labyrinth zone. This increase of H-FABP mRNA levels from day 13 to day 21 indicates its potential role in the enrichment of LC-PUFAs, especially DHA in brain, during the latter stage of pregnancy to meet the demand of rapid brain growth [87]. Compared with H-FABP, the liver isoform is more efficient in taking up fatty acids from liposomes in human placenta [94].

2. Fatty acid translocase (FAT/CD36) in placenta

FAT/CD36 is also present in human placenta within the placental membranes, microvillus and basal membranes. Distinct from the asymmetrical distribution of fatty acid-binding protein on membranes, FAT/CD36 localized on both sides of bipolar placental cells and binds long-chain fatty acids without preference for any particular fatty acids [96].

3. Fatty acid-transport proteins (FATPs) in placenta

Three isoforms of FATPs (FATP1, FATP4 and FATP6) have been identified in human placental membranes [97]. FATP4 is highly expressed in cultured trophoblasts [98]. Expression of placental FATP4 mRNA is positively correlated with the fetal DHA uptake into placental and cord blood phospholipids, suggesting its participation in selective materno-fetal DHA transfer in humans [97]. Targeted deletion of FATP4 leads to early embryonic lethality [99]. Activation of PPAR and/or RXR enhances the expression of FATP1 and FATP4, as well as potentiates the uptake and accumulation of fatty acids in *via* a p38 MAPK-dependent pathway in primary human trophoblasts. Inhibition of p38 MAPK not only down-regulates the expression of FATP4, but also blocks PPAR and RXR activation-induced increases in fatty acid transport into trophoblasts [100, 101]. Lethality of FATP4-deficiency in mice further suggests the necessity of FATP4 in fetal growth and development [99].

Although plenty of proteins facilitate the transportation of fatty acids across the placenta, the mechanism of PUFA accumulation in the fetus is still uncertain. Moreover, various factors influence the accumulation of LC-PUFAs in fetus. For example, sex hormones may regulate the expression of desaturases, DHA conversion is more efficient in the liver of females, and females have higher circulating concentrations of DHA [102, 103].

Fatty acid transportation-related proteins in aging

1. Expression of FABPs in aging

The lipid fatty acid composition in and fluidity of brain membranes change in an age-dependent manner. Fatty acid transportation-related proteins, including the binding proteins FABPs, have been shown to be involved in fatty acid uptake, metabolism, and distribution in brain throughout the lifetime. FABPs mRNA expression levels systematically decrease by 2–3 fold between P14–P21 and P60. In particular, FABP7 mRNA abundance is the most affected by 10 fold [104]. In addition, mouse brain levels of H-FABP and B-FABP are not evenly expressed in different subcellular fractions, with B-FABP expressed at lower levels compared to H-FABP. In aged mouse brain (25-month-old), the expression of H-FABP in synaptosomes, synaptosomal cytosol, and intrasynaptosomal membranes is reported to decrease 33, 35 and 43% respectively, while B-FABP decreases in synaptosomes, synaptic plasma membranes, and synaptosomal cytosol, but is not detectable in the intrasynaptosomal membranes. Enrichment of synaptosomal cytosol decreases with aging for both H-FABP and B-FABP. In addition, the age-associated decrease in B-FABP is nearly twofold greater than H-FABP. A relationship may exist between decreased brain H-FABP and B-FABP levels and altered membrane fatty acid composition and/or fatty acid function with aging. Aging-associated modifications of FABPs expression levels in brain may be an important factor in cellular dysfunction in central nervous system (Figure 4) [27]. In contrast to FABP expression, FABP binding activity increases in an age-dependent manner, and is much higher in white matter compared to gray matter at all ages [104]. Specifically, the FABP5 is downregulated in the RPE/choroid complex in aging and early age-related macular degeneration [105].

2. FABPs in aging and dementia

FABPs are potential sensitive biomarkers for minor brain injury. Levels of H-FABP are significantly increased in cerebrospinal fluid (CSF) and serum in dementia patients with Lewy-bodies (DLB) and Alzheimer's disease (AD) [106, 107]. The presence of H-FABP in both CSF and serum, in combination with tau protein in CSF, have potential to act as a differential diagnostic tool between DLB and AD [108]. Interesting, Creutzfeld Jacobs disease (CJD) patients have the highest levels of H-FABP in CSF and plasma, which may serve as a diagnostic biomarker for this disease [107]. Contrary to its elevation in CSF and serum, H-FABP is decreased in frontal, occipital and parietal cortices regions in brain of patients with Down syndrome and AD [109]. Besides H-FABP, another member of the FABP family B-FABP is elevated in serum of patients with AD, Parkinson's disease and other cognitive disorder (OCD) [109, 110].

3. FAT/CD36 in Alzheimer's disease

FAT/CD36 is a class B scavenger receptor expressed by microglia and vascular endothelial cells in the normal brain. Its expression is significantly increased in aged brains presenting with diffuse amyloid plaques and the brains of AD patients. Despite the increase observed in AD brain, FAT/CD36 is decreased in peripheral leukocytes in patients with mild cognitive impairment and AD [111–113]. FAT/CD36 participates in binding to fibrillar Aβ (fAβ) and the production of reactive oxygen species (ROS) by microglia, indicating a potential role in the inflammatory response in AD brain [114]. Knockout of CD36 reduces the response of microglia to fAβ, with less macrophage and microglial recruitment to fAβ injection sites *in vivo,* and is associated with decreased secretion of ROS, cytokines and chemokines *in vitro* [115]. CD36 can bind with Aβ, alpha(6)beta(1)-integrin and CD47, and heparan sulfate proteoglycans to form a complex in glial cells, which may contribute to the development of AD [116]. Interestingly, CD36 can also be stimulated by IL-4, which contributes to the uptake and degradation of oligomeric Aβ [117], proposing then that CD36 may also exert a beneficial role in the clearance of Aβ. FAT/CD36 is not only present in macrophages but also on neurons. Aβ exposure induces CD36 expression in neurons, indicating its early involvement in response to toxic Aβ [111, 118]. The potential for multiple functions of FAT/CD36 in the development of AD deserves further investigation.

Fatty acid transportation-related proteins in stroke

1. FABP in cerebral ischemia

FABPs are novel and promising serum markers of tissue injury [119]. B-FABP is expressed by neuroepithelial precursor cells in the developing brain and immature astrocytes, while not detectable in serum of healthy subjects [120]. H-FABP is predominantly expressed in neuronal cell bodies, and is expressed at levels >10 fold higher than B-FABP in tissue contents [120]. Clinical observations following stroke have demonstrated that B-FABP and H-FABP concentrations reach peak value as soon as 2–3 hours post-stroke and remain at high concentrations up to 5 days following stroke [121], indicating their potential role as molecular markers for the diagnosis of stroke. In primates, B-FABP is primarily expressed in astrocytes and progenitors of the subgranular zone, while E-FABP is normally detected in neurons and increased in CA1 following cerebral ischemia [122]. E-FABP and B-FABP, but

not H-FABP, are significantly increased on day 15 after cerebral ischemia in hippocampal SGZ, arguing for a role in regulating neurogenesis of hippocampal neurons in the adult brain [122, 123]. To this end, FABP-mediated transportation of DHA may cooperate with GPR40-pCREB-BDNF signaling pathway to stimulate adult neurogenesis in primates after cerebral ischemia [124–126].

2. FAT/CD36 in cerebral ischemia

Ischemic stroke induces the production of CD36 as well as its ligands, including oxLDL, long-chain fatty acids, Aβ and thrombospondin-1 [127, 128]. Hyperlipidemia exacerbates ischemic stroke outcomes via stimulating the expression of CD36 in the post-ischemic brain as well as in peripheral macrophages [70]. In addition, CD36 facilitates the production of free radical production during the post-ischemic phase [128]. CD36 is also expressed in glial scar-forming astrocytes in the penumbra [128]; consistently, in CD36 knockout mice, stroke-induced proliferation of astrocytes and scar formation is reduced [129]. Infiltration of peripheral immune cells is the major source of CD36 in the post-ischemic brain and contributes to stroke-induced brain damage [130, 131]. Knockout of CD36 in mice reduces microglial activation and neutrophil infiltration that is associated with TLR2/6 but not TLR2/1 activation after cerebral ischemia, suggesting that CD36 is required for the activation of TLR2/1 signaling pathway [132]. Genetic deletion of CD36 in hyperlipidemic conditions reduces proinflammatory chemokines/receptors and cytokines in the brain 6 hours after transient cerebral ischemia [70]. However, CD36 deficiency is not protective against permanent ischemic stroke [133]. In neonates, lack of CD36 results in poor short-term neurological outcomes partially due to dysregulation of toll-like receptor 2 (TLR2) expression and alteration of microglia phenotypes after ischemic stroke [134, 135].

3. FABP in cerebral hemorrhage

Subarachnoid hemorrhage (SAH) is associated with a significant increase in CSF H-FABP concentrations related to the severity of the disease. In addition, the occurrence of clinical vasospasm is correlated with an increased H-FABP and tau proteins; specifically, higher H-FABP and tau levels are detected in patients with worsened neurological outcomes [136]. Another notable value of biomarkers lies in their utilization for both the investigation into mechanisms of secondary brain damage as well as the recognition of new cerebral complications. In patients, urinary L-FABP can act as a biomarker for use in at-risk patients to monitor for cerebral hemorrhage, myocardial infarction, angina pectoris, stroke future renal failure and incidence of early stage diabetic nephropathy related to type 2 diabetes [137].

4. FAT/CD36 in cerebral hemorrhage

Hematomas, which are formed after an intracerebral hemorrhage (ICH), are the primary cause of neurological deficits after ICH. Effective hematoma removal is beneficial for alleviating mechanical compression, inhibiting inflammatory damage, and promoting the recovery of neuronal function [138, 139]. FAT/CD36, a type II scavenger receptor, plays an important role in mediating phagocytosis. A TLR4 inhibitor significantly upregulates CD36 expression in microglia, leading to increased phagocytic capacity of microglia and facilitating hematoma absorption in ICH mice [140]. Stimulation of PPARγ also upregulates

the expression of CD36, which facilitates hematoma resolution and ameliorates long lasting neurological deficits after hemorrhage (Figure 5) [141, 142].

Conclusion

Polyunsaturated fatty acids are extremely important for the development of brain and maintaining neurological functions into adulthood. The uptake of fatty acids is dependent on albumin and other fatty acids transportation-related proteins, including FATPs, FABPs, Mfsd2a and FAT/CD36. Expression levels of these proteins change with age and greatly impact the cerebral concentration of fatty acids, especially polyunsaturated fatty acids. These proteins appear to be involved in neurological disorders in both a fatty acids intake-dependent or -independent manner. Fatty acids transportation-related proteins may be potential therapeutic targets of neurological diseases.

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Highlights

- Explore metabolism of polyunsaturated fatty acids in mammals affecting cerebral levels
- Illustrate the accumulation of PUFAs required for fetal development relies on dynamic role of transportation proteins between placenta and fetus
- Detail the potential use of fatty acid transportation related proteins as biomarkers and potential mediators of aging, dementia and cerebral injury

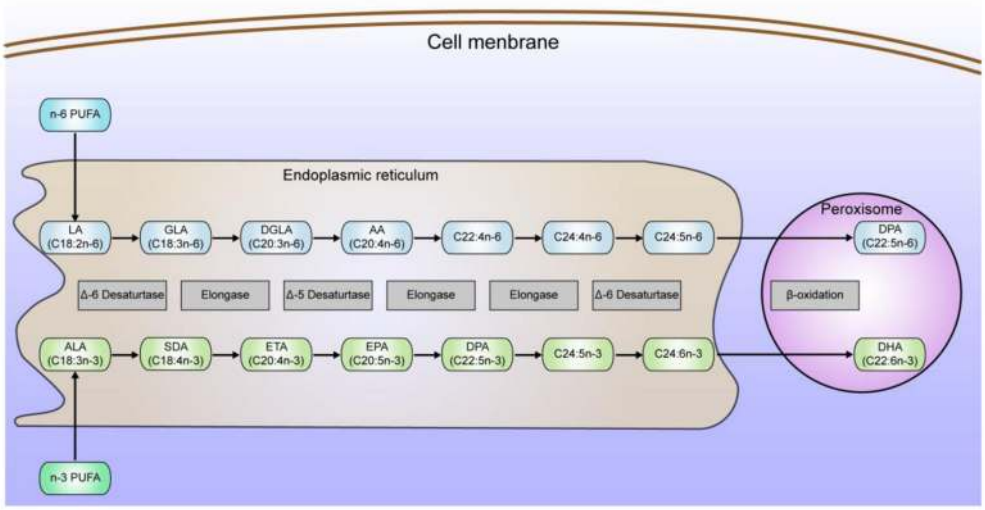

Figure 1. Biosynthesis of long chain unsaturated fatty acids from 18-carbon precursors in mammals

Most of the body's tissue can construct 20-carbon unsaturated fatty acids and 22-carbon unsaturated fatty acids from the corresponding 18-carbon fatty acids precursors by elongation and desaturation. This process mainly occurs in the endoplasmic reticulum, followed by the final oxidation in the peroxisome. LA linoleic acid; GLA γ-linolenic acid; DGLA dihomo-γ-linolenic acid; AA arachidonic acid; C22:4n-6 arenic acid; C24:4n-6 tetracosatetraenoic acid; C24:5n-6 Tetracosapentaenoic acid; ALA α-linolenic acid; SDA stearidonic acid; ETA eicosatetraenoic acid; EPA eicosapentaenoic acid; DPA docosapentaenoic acid; DHA docosahexaenoic acid.

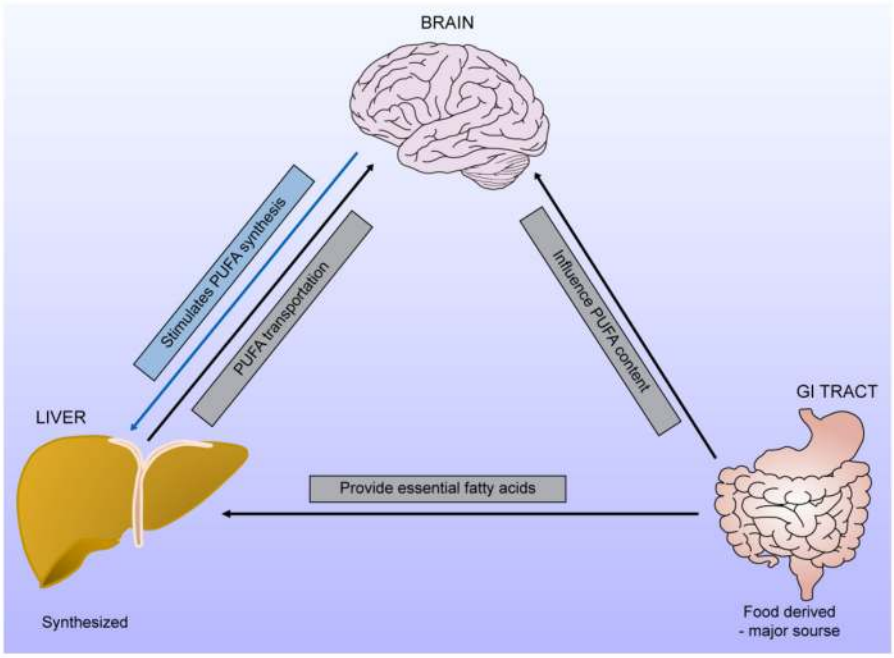

Figure 2. The source of cerebral PUFAs

Cerebral PUFAs are mainly derived from diet. The liver is considered to be a primary site that produces DHA, EPA and AA from their dietary precursors, and then releases them to the blood flow to supply other tissues. Dietary restriction of n-3 PUFAs stimulates the synthesis of DHA from its precursor ALA in liver to maintain the content of PUFAs in brain.

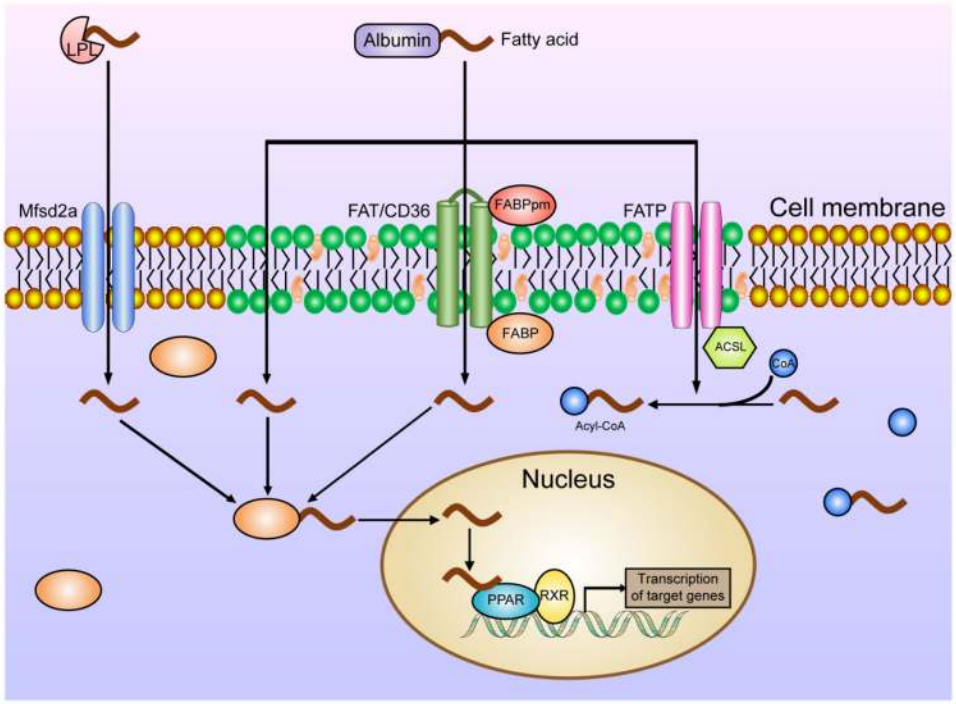

Figure 3. Uptake of PUFAs in brain

PUFAs are carried through the plasma by albumin and circulating lipoproteins, and, after release from these proteins, PUFAs bind to the luminal surface of endothelial cells, integrate into the external phospholipid bilayers as uncharged molecules, and then translocate to the inner leaflet of phospholipid bilayers by flip-flop or by a transporter-dependent manner. There are four classes of lipid transportation proteins involved in lipid synthesis and transportation in adult brain, including fatty acid translocase (FAT/CD36), fatty acid binding proteins (FABPs) with long chain acyl-coA synthase (ACS) activity, fatty acid transportation proteins (FATPs) and major facilitator superfamily domain-containing protein (Mfsd2a). In cerebral endothelial cells, these fatty acids repeat the flip-flop process and go through the abluminal membrane of endothelia with the aid of FABP. Cytosolic FABPs prevent the oxidation of unsaturated fatty acids, and facilitate the transportation of fatty acids to nuclear receptors such as PPARs, where they demonstrate gene regulatory activities in neurons.

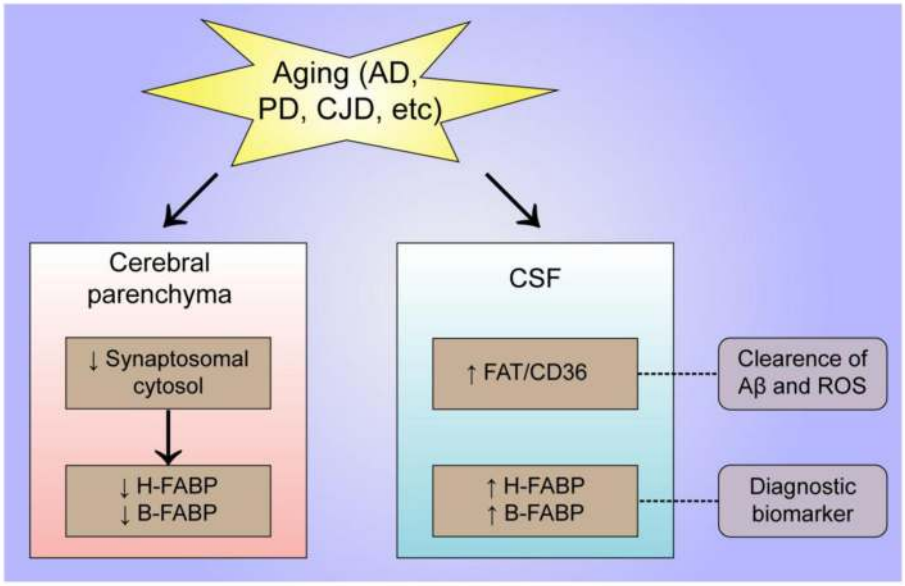

Figure 4.

The levels of brain H-FABP and B-FABP in synaptosomes and synaptosomal cytosol decrease with the increase in age, while their protein levels increase in both the cerebrospinal fluid (CSF) and serum of patients with dementia with Lewy-bodies (DLB) and Alzheimer's disease, indicating their potential role as a biomarker for dementia-related diseases. Elevation of FAT/CD36 is related to ROS production and clearance of Aβ in the brains of patients with Alzheimer's disease.

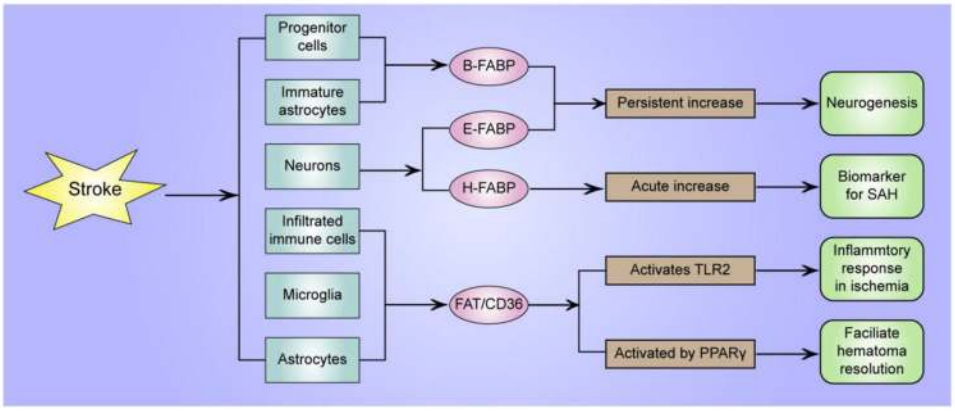

Figure 5. The role of fatty acids transportation related proteins in stroke

B-FABP is expressed in neuroepithelial precursor cells of the developing brain and immature astrocytes, while E-FABP and H-FABP are normally detected in neurons. As molecular markers for the diagnosis of stroke, B-FABP and H-FABP concentrations reach peak value within 3 hours after stroke onset. Persistent increase of cerebral B-FABP and E-FABP in brain regions of proliferation suggests a potential role in neurogenesis after cerebral ischemia. CSF H-FABP levels are associated with the severity of subarachnoid hemorrhage. FAT/CD36 is mainly expressed in peripheral infiltrating immune cells after stroke, but also is found in microglia and astrocytes. CD36 is required for the activation of TLR2 signaling pathway to regulate inflammatory responses after cerebral ischemia, and is upregulated by the activation of PPARγ to facilitate hematoma resolution following cerebral hemorrhage