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Review article

Fatty acid binding proteins and the nervous system: Their impact on mental conditions

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ABSTRACT

The brain is rich in lipid and fatty molecules. In this review article, we focus on fatty acid binding proteins (Fabps) that bind to fatty acids such as arachidonic acid and docosahexianoic acid and transfer these lipid ligands within the cytoplasm. Among Fabp family molecules, Fabp3, Fabp5, and Fabp7 are specifically localized in neural stem/progenitor cells, neurons and glia in a cell-type specific manner. Quantitative trait locus analysis has revealed that Fabp7 is related with performance of prepulse inhibition (PPI) that is used as an endophenotype of psychiatric diseases such as schizophrenia. Fabp5 and Fabp7 play important roles on neurogenesis and differentially regulate acoustic startle response and PPI. However, other behavior performances including spatial memory, anxiety-like behavior, and diurnal changes in general activity were not different in mice deficient for Fabp7 or Fabp5. Considering the importance of fatty acids in neurogenesis, we would like to emphasize that lipid nutrition and its dynamism via Fabps play significant roles in mental conditions. This might provide a good example of how nutritional environment can affect psychiatric conditions at the molecular level.

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1. Introduction

Lipids are major components of the brain. This is because cells consisting the brain such as neurons and glia cells have a high cell membrane/cytoplasm ratio due to their complex morphology with many processes. Since the cell membrane is formed as a lipid bilayer, the molecules including saturated and unsaturated fatty acids and cholesterols are the major component of the brain (Bourre et al., 1992; Zerouga et al., 1991). Lipids are also important as nutrients because they have high calorific value, compose

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biological structures, and produce biologically active substances. Lipids often become more easily deficient than other nutrients such as carbohydrates among various nutritional components in the malnutrition caused by severe famine. Therefore, abnormal diet in terms of excess intake or shortage of lipid nutrients and/or imbalance of the lipid composition may cause malfunctions of the brain. In this manuscript, we focus on fatty acids and fatty acid binding proteins with regard to mental illness.

2. Players in fatty acid signaling

Fatty acids are not only major components of the cell membranes but also effective energy sources for oxidation in the mitochondria and peroxisomes. Moreover, some fatty acids act as signaling molecules, which lead to a variety of physiological responses. Among polyunsaturated fatty acids (PUFAs), *n*-3 and *n*-6 PUFAs have been most studied on their biological functions. An *n*-3 PUFA, docosahexaenoic acid (DHA), and *n*-6 PUFA, arachidonic acid (ARA), are major components in the brain (Sastry, 1985). In neurons, particularly, the ARA is released from the cell membrane by a membrane-bound enzyme, phospholipase A2, in the neuronal activity-dependent manner (Bazan et al., 1993; Stella et al., 1995). Released ARA is metabolized into other bioactive substances such as prostagandins by enzymes such as cyclooxygenases, leading to various physiological functions (Oomagari et al., 1991).

Fatty acids also play important roles as signaling molecules in the lipid signaling pathways regulating the gene expression related to lipid and carbohydrate metabolism. Fatty acids taken from diets are present as free fatty acids binding to a carrier protein such as albumin or triglyceride/phospholipid/lipoprotein complex in blood, and delivered to various tissues including liver, adipocytes, and brain via blood circulation (Jacome-Sosa and Parks, 2014; Picq et al., 2010; Voshol et al., 2009). Since PUFAs cannot be easily soluble within the aqueous conditions, they need to bind to albumin protein within blood plasma (Richieri et al., 1993) and to fatty acid binding proteins (Fabps) within the cytoplasm (Fig. 1). Regarding fatty acid signaling, in which lipid ligands such as PUFAs act its upstream, Fabps play central roles as intracellular carriers to transport the PUFAs to various regions within the cytoplasm (Furuhashi and Hotamisligil, 2008; Liu et al., 2010). In liver and adipocytes, for example, fatty acids are shuttled from the cytosol to the nucleus by Fabps, and modulate gene expression by binding to transcription factors such as peroxisome proliferator-activated receptors (PPARs), a member of nuclear hormone receptor family (Atshaves et al., 2010; Schroeder et al., 2008). Fatty acids, especially ARA and DHA are converted into various eicosanoids and behave as signaling molecules related with inflammation (Tam, 2013).

To date, at least 10 genes encoding FABPs have been identified in the human genome (FABP1–9, and FABP12) (Fig. 2) (Smathers and Petersen, 2011). FABPs show a wide range of homology (between 20 and 70% in amino acid sequences) but high tertiary structures (Storch and Thumser, 2010). Most of the Fabps bind to single long chain fatty acids except for Fabp1, which binds to two fatty acids (Atshaves et al., 2010). Fabp expression is distributed through

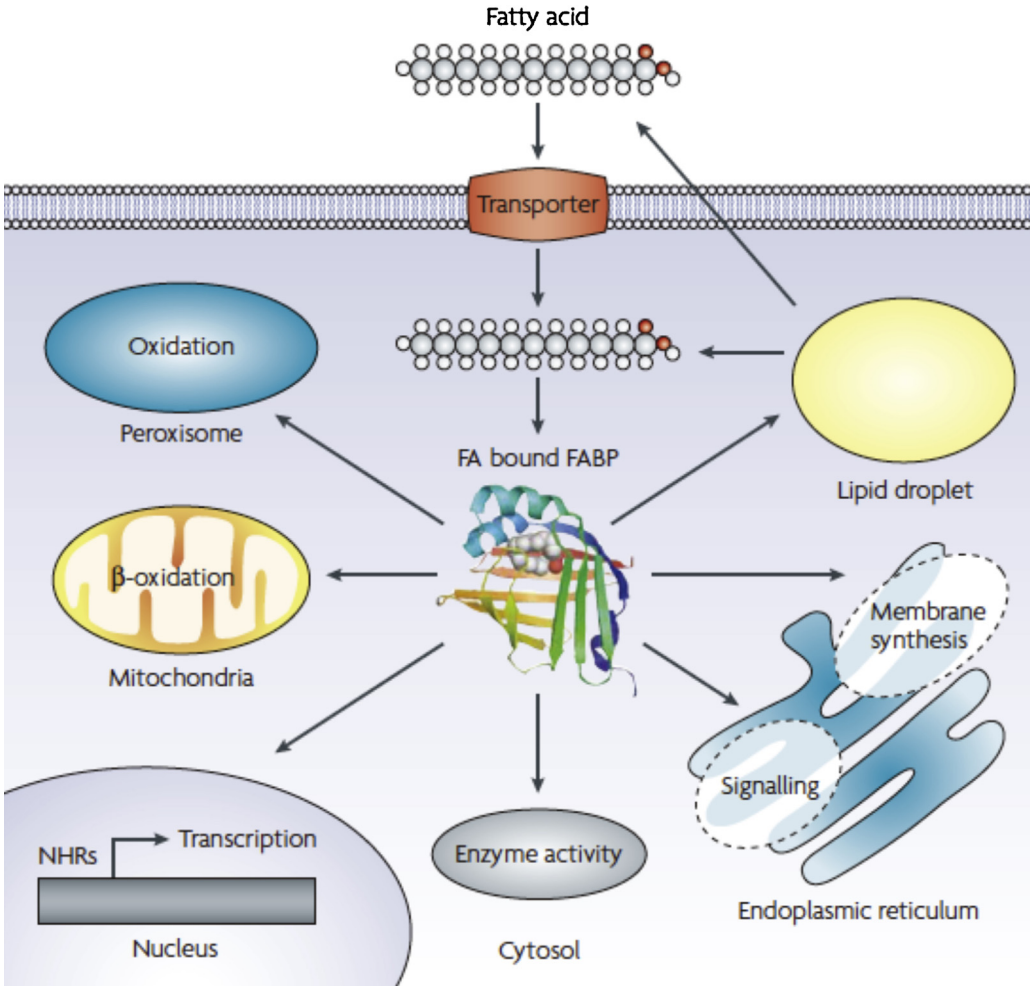

Fig. 1. Fabp is a cytoplasmic shuttle molecule. Fabp binds to fatty acid and deliver the fatty acid to various organella within a cell, thereby playing pivotal roles in energy production, membrane synthesis, lipid droplet deposition, and gene expression. Illustration is modified from Fig. 1 in reference Furuhashi and Hotamisligil (2008).