Published in final edited form as:
Brain Res. 2015 February 9; 0: 220–246. doi:10.1016/j.brainres.2014.11.059.

Pathways of Polyunsaturated Fatty Acid Utilization: Implications for Brain Function in Neuropsychiatric Health and Disease

Joanne J. Liu, M.S.[1,2], **Pnina Green, M.D., Ph.D.**[3], **J. John Mann, M.D.**[1,4,5], **Stanley I. Rapoport, M.D.**[6], and **M. Elizabeth Sublette, M.D., Ph.D.**[1,4,*]

[1]Department of Molecular Imaging & Neuropathology, New York State Psychiatric Institute, NY, NY

[2]New York Medical College, Valhalla, NY

[3]Laboratory of Metabolic Research, Felsenstein Medical Research Center, Tel Aviv University, Petach Tikva, Israel

[4]Department of Psychiatry, Columbia University, NY, NY

[5]Department of Radiology, Columbia University, NY, NY

[6]Brain Physiology and Metabolism Section, Laboratory of Neuroscience, National Institute on Aging, National Institutes of Health, Bethesda, MD

Abstract

Essential polyunsaturated fatty acids (PUFAs) have profound effects on brain development and function. Abnormalities of PUFA status have been implicated in neuropsychiatric diseases such as major depression, bipolar disorder, schizophrenia, Alzheimer's disease, and attention deficit hyperactivity disorder. Pathophysiologic mechanisms could involve not only suboptimal PUFA intake, but also metabolic and genetic abnormalities, defective hepatic metabolism, and problems with diffusion and transport. This article provides an overview of physiologic factors regulating PUFA utilization, highlighting their relevance to neuropsychiatric disease.

Keywords

Polyunsaturated fatty acids; lipid metabolism; brain; depression; bipolar disorder; schizophrenia

[*]To whom correspondence should be addressed: New York State Psychiatric Institute, 1051 Riverside Drive, Unit 42, NY, NY 10032, Tel: (646) 774 – 7514, Fax: (646) 774 – 7589, es2316@columbia.edu.

Conflicts of Interest
All other authors have no conflicts of interest to report.

1. INTRODUCTION

Lipids, which compose cell membranes, occur in very high concentrations throughout the central nervous system (Jumpsen, 1995), making up about half the dry weight of the human brain (Benatti et al., 2004). Of brain lipids, approximately 35% are polyunsaturated fatty acids (PUFAs), which cannot be synthesized de novo from 2-carbon fragments and are nutritionally essential (Benatti et al., 2004). PUFAs are critical for normal brain development and functioning (Luchtman and Song, 2013). They fall into three major categories, according to the number of carbon atoms separating the first double bond of the carbon chain from the terminal methyl (omega) end: n-3, n-6, and n-9. This review will focus primarily on three highly unsaturated, long-chain PUFAs (LC-PUFAs) that appear relevant to neuropsychiatry: arachidonic acid (AA, 20:4n-6) and docosahexaenoic acid (DHA, 22:6n-3), which make up 50% and 40% of brain PUFAs, respectively (Gerster, 1998; Lauritzen et al., 2001; Singh, 2005; Spector, 1999); and eicosapentaenoic acid (EPA, 20:5n-3) (Fernstrom, 1999; McNamara and Strawn, 2013; Youdim et al., 2000; Young and Conquer, 2005), which is maintained at a much lower brain concentration (Chen et al., 2009; Chen et al., 2011) through very rapid breakdown by β-oxidation (Chen and Bazinet, 2014). Also relevant are n-6 and n-3 isomers of docosapentaenoic acid (DPA, 22:5), both of which may serve as a partial substitute for DHA in states of experimental n-3 PUFA deficiency (Kaur et al., 2010; Kaur et al., 2011; Lim et al., 2005b); and linoleic acid (LA, 18:2n-6) and alpha-linolenic acid (ALA,18:3n-3), the shorter-chain nutritionally essential precursors of longer-chain n-6 and n-3 PUFAs, respectively.

Lipidomics in neuropsychiatric illness is an emerging field (Wenk, 2005). With respect to LC-PUFA, both AA and DHA are critical to brain development and maintenance of brain structure and function. DHA is important for the health of developing neurons and for neurotransmission, with clear ramifications for cognition and behavior (Innis, 2007). Neurological health also requires sufficient levels of AA for the growth (Darios and Davletov, 2006), repair (Darios and Davletov, 2006), maintenance (Fukaya et al., 2007), and protection (Wang et al., 2006) of neurons. The role of EPA in brain functioning is less clear, but it has been found to be an important component in PUFA supplements for treatment of depression (Lin et al., 2012; Martins, 2009; Martins et al., 2012; Sublette et al., 2011), and EPA status has been specifically associated with certain aspects of substance use disorders (Beier et al., 2014; Buydens-Branchey et al., 2011). Dysregulated lipid metabolism and low dietary consumption of n-3 PUFAs have been implicated in neuropsychiatric diseases, encompassing specific domains including development (Daniels et al., 2004; Gustafsson et al., 2004; Helland et al., 2003; Jorgensen et al., 2001; Larque et al., 2002; Milte et al., 2011; Veena et al., 2010), neurodegeneration (Conquer et al., 2000; Morris et al., 2003; Schaefer et al., 2006), cognition (Barberger-Gateau et al., 2007; Beydoun et al., 2007; Devore et al., 2009; Dullemeijer et al., 2007; Eskelinen et al., 2008; Heude et al., 2003; Huang et al., 2005; Kalmijn et al., 1997a; Kalmijn et al., 1997b; Kalmijn et al., 2004; Lopez et al., 2011; Morris et al., 2003; Morris et al., 2005; Schaefer et al., 2006; Tan et al., 2012; van Gelder et al., 2007), mood (Adams et al., 1996; Amin et al., 2008; Bountziouka et al., 2009; Conklin et al., 2007; Edwards et al., 1998; Frasure-Smith et al., 2004; Green et al., 2006; Hibbeln, 1998; Hibbeln, 2002a; Lin et al., 2010; Maes et al., 1999b; McNamara et al., 2010; Peet et

al., 1998; Raeder et al., 2007; Riemer et al., 2010; Sanchez-Villegas et al., 2007; Schins et al., 2007; Tanskanen et al., 2001), psychosis (Amminger et al., 2010; Evans et al., 2003a; Kaddurah-Daouk et al., 2007), suicidal behaviors (Huan et al., 2004; Lewis et al., 2011; Sublette et al., 2006), and neuroinflammation (Calder, 2006b; Kiecolt-Glaser et al., 2007).

The goal of this article is to review and integrate the scientific literature concerning aspects of PUFA physiology and metabolism that may influence neuropsychiatric diseases.

2. POLYUNSATURATED FATTY ACIDS

2.1. Sources of PUFAs

The average daily intake of total lipids by American adults is about 85g, comprising 33% of total energy intake (U.S. Department of Agriculture: Agricultural Research Service, 2008). Most lipids found in foods are in the form of triacylglycerols, while the remainder include cholesterol, cholesteryl esters, phospholipids, and nonesterified (free) fatty acids (Brown, 1991). N-3 and n-6 PUFAs are essential nutrients because they cannot be synthesized by vertebrates *de novo*; and the ALA and LA precursors, which can be converted to LC-PUFA in the liver and to some extent in other organs, must be obtained through direct dietary consumption (Burr, 1930).

LA, the parent compound of the n-6 family, and AA, the major brain n-6 species, are plentiful in nature. LA is found in the seeds of most plants such as soybean, canola, corn, sunflower, safflower, and cottonseed (some exceptions being coconut, cocoa and palm), whereas AA is found in most meats and products from animals fed corn-based diets high in n-6 PUFAs (Meyer et al., 2003; Simopoulos, 1999). ALA, the precursor for the n-3 PUFA family, is found in green leafy vegetables, walnuts, and the seeds of flax, rape, and chia (Sinclair et al., 2002). Seafood is currently the major source of EPA and DHA in most industrialized countries (Simopoulos, 2011), although significant amounts can be obtained through ingestion of protein from animals fed diets high in n-3 PUFAs, including eggs from n-3 PUFA-fed chickens (Trebunova et al., 2007) and beef from range-fed cattle (Howe et al., 2006; Ollis et al., 1999). According to Simopoulos (Simopoulos, 2011), changes in practices by the food industry have led to dramatic dietary imbalances, shifting from an approximately equal intake of n-6 to n-3 PUFAs 150 years ago to current ratios of about 20 to 1, a change that may contribute to modern health problems. Ironically, to some extent, this shift in PUFA balance also may be due to earlier efforts to improve public health through lowering cholesterol levels by replacing saturated fat intake with polyunsaturated fats, without an adequate understanding of the relative risks and benefits of altering the n-6 to n-3 PUFA balance, including the risks to mental health. For example, meta-analyses of mortality rates in studies of dietary interventions and in medication trials to lower cholesterol found no reduction of mortality rates, but rather increased mortality due to violent death such as suicide and accidents (Muldoon et al., 1990; Muldoon et al., 2001). A recent study suggests that elevated n-6 to n-3 PUFA ratios may be remedied by altering the diet with therapeutic benefit in brain disease (Ramsden et al., 2013).

At the present time, no official Dietary Reference Intake (DRI) criteria have been determined for LC-PUFAs in the US and Canada, as there are no agreed-upon normal ranges

or clinical functional endpoints for DHA or EPA (Panel on Macronutrients, 2002). However, it is clear that individuals living in the U.S. and many other countries whose diet is importantly derived from reared animals have a very low dietary n-3 PUFA intake compared with other, more seafood-oriented cultures. In a study showing that low DHA was associated with higher suicide risk among US military personnel, Lewis et al. (Lewis et al., 2011) note that almost the entire US military study population had lower DHA levels than the lowest group in a Chinese case-control study of suicide attempters (Huan et al., 2004). Cross-national comparisons find that lower intakes of seafood, by country, are associated with higher rates of bipolar disorders (Noaghiul and Hibbeln, 2003) and post-partum depression (Hibbeln, 2002b).

2.2. Long-chain PUFA structure and synthesis

The metabolic fate of an ingested fatty acid is influenced by the lipid in which it is esterified, and by its structural characteristics, which include carbon chain length, number of double bonds, placement of double bonds relative to the omega carbon, and configuration of hydrogen atoms around the double bonds (*cis* or *trans*).

The number of double bonds influences fatty acid flexibility at double bond locations (Gawrisch et al., 2003). This has implications for cell membrane lipid matrix properties, formerly referred to as ‘fluidity’ (Shinitzky and Barenholz, 1978), but more recently described in terms of ‘lipid rafts’ or ‘membrane microdomains’, dynamic membrane aggregations of specific lipid composition that promote interactions between membrane-bound proteins by bringing them into physical proximity (Pike, 2006; Yaqoob and Shaikh, 2010). The highly flexible n-3 PUFAs incorporate directly into membranes and thereby promote the partitioning of the more rigid cholesterol and sphingolipid moleclules into lipid rafts (Altenburg and Siddiqui, 2009; Duraisamy et al., 2007; Eldho et al., 2003; Grimm et al., 2011; Huster et al., 1998; Langelier et al., 2010; Rockett et al., 2012; Rogers et al., 2010; Schley et al., 2007; Shaikh et al., 2002; Shaikh et al., 2003; Shaikh et al., 2004; Soni et al., 2008; Stillwell et al., 2005a; Stillwell et al., 2005b; Wassall et al., 2004; Wong et al., 2009b; Ye et al., 2010).

The nutritionally essential shorter chain PUFAs LA and ALA undergo a series of desaturation and elongation steps (Mayes, 1996) in the endoplasmic reticulum and peroxisomes of the liver to form n-6 (AA) and n-3 (EPA and DHA) LC-PUFAs, respectively (Figure 1), catalyzed by enzymes that are upregulated in response to experimental deficiency of n-3 PUFAs (Rao et al., 2007b). The conversion process normally occurs with low efficiency (de Gomez Dumm and Brenner, 1975; Emken, 1989b) at rates of 0.2 to 21% (Burdge et al., 2002; Burdge and Wootton, 2002; Emken et al., 1994). However, in rats fed LC-PUFA-deficient diets, net conversion of LA to AA and ALA to DHA increases; even in severe deficiency, the amount of DHA produced greatly exceeds brain PUFA consumption (Domenichiello et al., 2014; Igarashi et al., 2006; Igarashi et al., 2007c; Rapoport and Igarashi, 2009). The applicability of these preclinical studies to humans is uncertain, but they suggest that in populations with low long-chain n-3 PUFA intake, such as vegans or vegetarians, the liver likely is capable of compensating and producing adequate DHA for brain function (Igarashi et al., 2007b; Igarashi et al., 2007c).

Several polymorphisms of the fatty acid desaturase gene cluster (*FADS1-FADS2*) (Cho et al., 1999a; Cho et al., 1999b) can affect production of LC-PUFAs from ALA and LA (Al-Hilal et al., 2013; Gillingham et al., 2013; Harslof et al., 2013; Koletzko et al., 2008; Malerba et al., 2008; Nwankwo et al., 2003; Rizzi et al., 2013; Schaeffer et al., 2006b; Solakivi et al., 2013), and thereby influence plasma concentrations of not only fatty acids, but also low density lipoprotein (LDL) and cholesterol (Tanaka et al., 2009). Postmortem studies have reported altered expression of genes regulating fatty acid biosynthesis in the prefrontal cortex of patients with schizophrenia (Liu et al., 2009a), major depressive disorder (McNamara and Liu, 2011), bipolar disorder (Liu and McNamara, 2011b), and depressed suicides compared with nonpsychiatric controls (Lalovic et al., 2010). Additionally, antipsychotic medications have been shown to upregulate mRNA expression of genes coding for biosynthetic enzymes in rats (Liu et al., 2009a; McNamara et al., 2011) and red blood cell PUFA levels in patients with psychosis (Evans et al., 2003a; Kaddurah-Daouk et al., 2007). *FADS2* expression is elevated in prefrontal cortex in schizophrenia, independently of sex or medication usage (Liu et al., 2009b). Decreased conversion of EPA to DHA has also been observed in schizophrenia (Mahadik et al., 1996).

2.3. The balance of n-3 and n-6 PUFAs

The n-3 and n-6 PUFA families often have opposing physiological functions, and therefore their relative proportions have implications for physiology and pathophysiology. In mammals, LA and ALA compete with each other for enzymes involved in the elongation – desaturation process (de Gomez Dumm and Brenner, 1975; Emken, 1989a; Hague, 1984a). Although the desaturation and elongation cascade is more selective for n-3 than n-6 PUFAs, due in part to higher affinities of Δ5 and Δ6 desaturases for n-3 PUFAs (de Gomez Dumm and Brenner, 1975; Hague, 1984b; Hague, 1986), high LA intake can interfere with the desaturation and elongation of ALA (Emken, 1989b; Indu, 1992) and slows hepatic synthesis of DHA (Smink et al., 2012), whereas *trans* fatty acids interfere with the desaturation and elongation of both LA and ALA (Simopoulos, 1994). In addition to dietary effects on the n-6 to n-3 PUFA balance, some physiologic states can influence long-chain n-3 PUFA production, including aging (de Gomez Dumm and Brenner, 1975), infant prematurity (Carlson et al., 1986), hypertension (Singer et al., 1984) and diabetes (Honigmann, 1982).

Conversely, enhanced PUFA catabolism could also contribute to PUFA imbalances. For instance, children with ADHD exhibit abnormal plasma fatty acid profiles (Colter et al., 2008) despite a dietary intake of LC-PUFAs equivalent to that of healthy children (Chen et al., 2004; Colter et al., 2008; Ng et al., 2009; Stevens et al., 1995). This difference could be explained by more rapid PUFA breakdown, because children with ADHD exhale higher levels of ethane, a non-invasive measure of oxidative damage to n-3 PUFAs (Ross et al., 2010). Increased catabolism of n-3 PUFAs has also been implicated in the pathology of schizophrenia (Evans et al., 2003b; Horrobin et al., 1994; Peet et al., 1995).

2.4. PUFA distribution

In mammals, the n-3 PUFAs are distributed selectively among lipid classes (Simopoulos, 2008). Both ALA and EPA are found in triacylglycerols and cholesteryl esters. However, in

phospholipids, ALA is minimally present, whereas DHA and EPA are both prominent components. In body organs, DHA is the most abundant n-3 PUFA, especially in brain and retina, where DHA is several hundred-fold more abundant than EPA (Arterburn et al., 2006). EPA is maintained at much lower brain concentrations (Chen et al., 2009; Chen et al., 2011) through rapid β-oxidation (Chen and Bazinet, 2014).

2.5. Overview of PUFA functions

PUFAs serve multiple important physiologic roles, falling within major categories that include energy storage and production, inflammation, and cell signaling, with effects on multiple organ systems. PUFAs impact energy by regulating lipid catabolism and lipogenesis (Kopecky et al., 2009), and PUFA metabolites serve as lipid mediators in endocrine, paracrine, and autocrine signaling within adipose tissue (Masoodi et al., 2014). Another mechanism of PUFA effects on cell signaling is the modulation of ion channel functioning, including sodium conductance in human and rodent ion channels in skeletal muscle (Wieland et al., 1992; Xiao et al., 1997) and calcium conductance in cardiomyocytes (Akhtar Khan, 2010; Chapkin et al., 2009; Ferrante et al., 1994; Kim et al., 2010; Reynolds and Roche, 2010; Szentandrassy et al., 2007; Triboulot et al., 2001; Yog et al., 2010) and T-cells (Triboulot et al., 2001; Yog et al., 2010)

Many effects of PUFAs can be attributed to their ability to regulate gene expression by affecting transcription factors (Jump, 2002; Jump et al., 2008a). Hepatic gene transcription factors affected by n-3 PUFAs include peroxisome proliferatoractivated receptor alpha, PPAR-α; sterol regulatory element-binding protein 1, SREBP-1; carbohydrate-responsive element-binding protein, ChREBP; and max-like protein X, MLX. These factors contribute to control of proteins involved in lipid synthesis and oxidation, and lipoprotein secretion (Jump et al., 1994; Jump et al., 2008b; Ntambi and Bene, 2001; Sessler and Ntambi, 1998). In cultured rat cardiomyocytes, supplementation with n-3 PUFAs causes up- and downregulation of genes related to lipid metabolism, inflammation, cell survival, cell proliferation, and cardiac contractility (Bordoni et al., 2007).

A deeper explanation for n-3 PUFAs' widespread effects is their ability to modulate membrane functioning at a subcellular level through influencing lipid rafts (Brown and London, 2000; Chapkin et al., 2008; Fan et al., 2003; Fan et al., 2004; Kim et al., 2008a; Ma et al., 2004; Pike, 2003; Smart et al., 1999). For example, DHA has robust effects on structural and dynamic characteristics of membrane domains (Huster et al., 1998; Shaikh et al., 2002; Shaikh et al., 2003; Shaikh et al., 2004; Soni et al., 2008; Stillwell et al., 2005b; Turk and Chapkin, 2012; Wassall et al., 2004; Williams et al., 2012) such as domain size and membrane order, likely due to lateral segregation of DHA-rich membrane domains from cholesterol-rich membrane regions. The physiologic implications for neuropsychiatry are profound, since such microdomains participate in regulation of serotonin (Magnani et al., 2004; Samuvel et al., 2005), dopamine (Adkins et al., 2007; Jones et al., 2012), and norepinephrine (Jayanthi et al., 2004; Matthies et al., 2009) transporters; serotonin 1A (Kalipatnapu and Chattopadhyay, 2005; Kobe et al., 2008; Nothdurfter et al., 2011; Pucadyil and Chattopadhyay, 2004; Renner et al., 2007; Sjogren et al., 2008), 2A (Dreja et al., 2002; Mialet-Perez et al., 2012; Sommer et al., 2009), 3A (Eisensamer et al., 2005; Ilegems et al.,

2005; Nothdurfter et al., 2010), and 7A (Sjogren et al., 2006; Sjogren and Svenningsson, 2007a; Sjogren and Svenningsson, 2007b) receptors; dopamine uptake (Jones et al., 2012); and dopamine D_2 receptor oligomerization (Celver et al., 2012; Genedani et al., 2005).

N-3 PUFAs also consistently have been implicated in lipid raft regulation of immunomodulation (Ariel et al., 2005; Basiouni et al., 2012; Baumer et al., 2010; Bonilla et al., 2010; Chentouf et al., 2010; De Smedt-Peyrusse et al., 2008; Diaz et al., 2002; Geyeregger et al., 2005; Gurzell et al., 2013; Hou et al., 2012; Kim et al., 2008b; Li et al., 2005; Li et al., 2007; Li et al., 2008; Murakami et al., 2012; Ruth et al., 2009; Schumann et al., 2011; Teague et al., 2013; Van Laethem and Leo, 2002; Webb et al., 2000; Wong et al., 2009a; Zeyda et al., 2002), including a direct influence on lipid raft modulation of Toll-like receptor 4, a factor governing induction of genes that regulate inflammatory responsiveness (Wong et al., 2009a).

3. DIGESTION, ABSORPTION, AND SECRETION OF DIETARY PUFAS

3.1. Oral detection of dietary PUFAs

The discovery of lipid receptors CD36 and GPR120 in taste bud cells supports the existence of a gustatory oral perception of dietary lipids (Degrace-Passilly and Besnard, 2012; Martin et al., 2011a; Nozaki et al., 1995). CD36 can bind PUFAs with nanomolar affinity (Baillie et al., 1996), and inactivation of the CD36 gene disturbs the consumption of PUFAs (Laugerette et al., 2005; Martin et al., 2011b). Human data also indicate that unesterified free fatty acids are taste stimuli that can be distinguished by chain length (Chale-Rush et al., 2007a; Chale-Rush et al., 2007b) and saturation (Mattes, 2009). Taste cues from the oral detection of lipids modulate subsequent lipid responsiveness (Mattes, 2005), e.g. meals with different fatty acid profiles (Fielding et al., 1996) differentially initiate mobilization of fat from jejunal enterocytes (Robertson et al., 2003).

3.2. Digestion of PUFAs

Digestion of lipids is catalyzed by lingual lipase (Hamosh et al., 1975) and gastric lipase (Armand, 2007), both of which hydrolyze the stereospecifically numbered (sn)-3 position of triacylglycerols (Staggers et al., 1981), producing free fatty acids, diacylglycerols, and a few 2-monoacylglycerols (Phan and Tso, 2001). The long-chain free fatty acids released by gastric lipolysis stimulate cholecystokinin secretion, which in turn stimulates pancreatic lipase secretion, slows gastric emptying (Hamosh, 1990), and suppresses appetite (Little et al., 2007).

Carbohydrate (amylose)-lipid complexes in the stomach may serve as a delivery system for PUFAs (Lalush, 2005). Following enzymatic hydrolysis of the amylose, these complexes facilitate optimal release of PUFAs into the small intestine (Lalush, 2005), where most lipid digestion takes place.

In the duodenum, emulsification of dietary lipids increases the surface area of hydrophobic lipid droplets for digestive enzymes (Bauer, 2005). Emulsion is accomplished through mechanical mixing by peristalsis in the presence of bile salts, amphipathic derivatives of cholesterol (Holt, 1971). Although lipid absorption is markedly more efficient in the

presence of bile, PUFAs, which are unsaturated, and therefore less hydrophobic, do not rely on bile for emulsification in the intestine as much as their saturated counterparts (Bernard and Carlier, 1991; Carlier et al., 1991; Demarne et al., 1982; Jones et al., 1985; Ockner et al., 1972; Toorop et al., 1979; Tso, 1994).

Hydrolysis of triacylglycerol into monoacylglycerol and free fatty acids is accomplished predominantly by pancreatic lipase (Bauer, 2005) which cleaves triacylglycerols at the sn-1 and sn-3 positions. Pancreatic lipase acts on EPA and DHA less than on shorter-chain fatty acids in the sn-3 position (Ikeda et al., 1995).

3.3. Absorption and secretion of PUFAs

Absorption of free fatty acids and 2-monoacylglycerol, the primary products of lipid digestion in the small intestine, is facilitated by formation of amphipathic mixed micelles, which carry their hydrophobic cargo across the enterocyte brush border membrane by simple diffusion (reviewed in (Ramirez et al., 2001). Short- and mediumchain length fatty acids do not require incorporation into mixed micelles for absorption. Triacylglycerol structure can also influence intestinal absorption, and fatty acids located in the sn-2 position can dramatically enhance absorption (Ramirez et al., 2001).

The mechanisms by which PUFAs are taken up by the enterocyte across its apical membrane likely include both facilitated (Abumrad et al., 1993; Chow and Hollander, 1979a; Chow and Hollander, 1979b; Diede et al., 1992; Hollander et al., 1984; Masson et al., 2010; Stremmel, 1988b) and passive diffusion (Chow and Hollander, 1979a; Ling et al., 1989). Uptake of PUFAs by facilitated membrane translocation involves fatty acid translocases (FAT) also known as CD36 (Abumrad et al., 1993; Diede et al., 1992; Stremmel, 1988b), fatty acid transport proteins (FATP), also known as very long-chain acyl-CoA synthetase (ACSVL) (Jia et al., 2007), and membrane-bound fatty acid binding proteins (FABP) (Masson et al., 2010).

Once inside the enterocyte, cytosolic FABP (FABPc) facilitates fatty acid transport (Storch and Corsico, 2008) to the smooth endoplasmic reticulum, where complex lipids are re-synthesized. Fatty acyl-CoA synthetase converts the fatty acids into activated acyl CoA derivatives that combine with 2-monoacylglycerols into triacylglycerols via the consecutive actions of acyl CoA:monoacylglycerol acyltransferase and acyl CoA:diacylglycerol acyltransferase, within the triacylglycerol synthase enzyme complex. The very hydrophobic triacylglycerols are re-packaged as chylomicrons and transported to the rest of the body via the lymphatic system (Fielding, 2008).

4. PERIPHERAL MECHANISMS OF PUFA TRANSPORT

4.1. Circulating lipoproteins

Lipids are transported within the plasma (Kane, 1983; Shen et al., 1977; Zilversmit, 1965) via lipoprotein particles composed of a neutral lipid core (triacylglycerol and cholesteryl esters) surrounded by a shell of amphipathic apolipoproteins, phospholipid, and nonesterified (free) cholesterol (Havel, 1975). In normal human serum, n-6 PUFAs account for 60% of fatty acids in cholesteryl esters, 22% in triacylglycerols, and 38% in

phospholipids (Edelstein, 1986). LA content ranges from 21–25% in phospholipids of the VLDL, LDL, and HDL fractions in subjects on an *ad lib* diet (Morrisett, 1976), while AA values are much lower, ranging from 4.8% in VLDL to 9.6% in HDL fractions. By contrast, n-3 PUFAs account for 1.7% in cholesteryl esters, 1.8% in triacylglycerols, and 3.5% in phospholipids, where DHA is the most abundant at 2.2%.

Chylomicrons are the largest and lowest density lipoproteins, containing the highest percentage of lipid, of which 90% is triacylglycerol (Jonas, 2008). As the chylomicron circulates, most of the triacylglycerol is hydrolyzed by lipoprotein lipase, and the particle decreases in size and increases in density until its remnant is endocytosed by the liver and degraded in lysosomes by hepatic lipase (Naik, 2011). The free fatty acids derived from the degradation of triacylglycerol may enter adjacent muscle cells or adipocytes, be β-oxidized for energy, or be transported in blood in association with albumin until cellular uptake occurs.

4.2. Hepatic processing of PUFAs

Chylomicrons and non-esterified circulating ALA and LA are taken up into hepatocytes from the circulation and serve as precursors for the synthesis of longerchain PUFAs (Demar et al., 2005; Igarashi et al., 2007a; Igarashi et al., 2008; Rapoport et al., 2010; Scott, 1989). Liver secretion of triacylglycerol-rich VLDL particles is dependent on the synthesis, activation, and esterification of acyl-CoA PUFA intermediates into phospholipids, triacylglycerols, or cholesteryl esters (Gibbons et al., 1992; Scott and Bazan, 1989; Vance and Vance, 1990). In addition, free fatty acids can be re-esterified into triacylglycerol molecules and stored in adipocytes and hepatocytes until release for body needs. This process, however, can result in pathological hypertriglyceridemia. N-3 PUFA supplementation in the form of fish oil is FDA-approved as a treatment for hypertriglyceridemia, suppressing both fasting and postprandial hypertriglyceridemia (Ikeda et al., 2001) by reducing hepatic triacylglycerol secretion (Agren et al., 1996; Hansen et al., 1998; Ikeda et al., 1998; Ikeda et al., 2001; Surette et al., 1992; Wong et al., 1984; Yoshida et al., 1999). Thus, lipid balance within the liver affects triacylglycerol concentrations and lipoprotein composition in plasma (Soutar, 1978) and, ultimately, in brain (Caspi et al., 2007).

Peroxisome proliferator-activated receptors (PPARs) in the liver play critical roles by translating nutritional stimuli (Berger and Moller, 2002), such as PUFA status, into changes in the expression and transcription rate of genes (Desvergne and Wahli, 1999; Kliewer et al., 2001; van Raalte et al., 2004), particularly those involved in lipid metabolism (Schoonjans et al., 1996).

PUFAs are the principal natural ligands for PPARα (Price et al., 2000; Sessler and Ntambi, 1998; van Raalte et al., 2004), expressed primarily in the liver, kidney, heart, muscle and adipose tissue. PPARα regulates the expression of proteins involved in transport and β-oxidation of free fatty acids (van Raalte et al., 2004). PUFAs and other PPAR α agonists also influence metabolism of lipoproteins, particularly triacylglycerol-rich lipoproteins (van Raalte et al., 2004). Genetic polymorphisms of PPARα can modulate the response of serum

lipid concentrations to dietary PUFA intake (Chan et al., 2006; Tai et al., 2005; Yamakawa-Kobayashi et al., 2002).

PPARα-stimulated fatty acid β-oxidation provides hepatocytes with an effective means for catabolism of fatty acids under conditions of fatty acid overload. Liver (L)-FABP is integral to this response and may act to reduce the toxicity of long-chain nonesterified fatty acids by binding them in the cytosolic compartment, thereby facilitating their intracellular diffusion and utilization (Bass, 1993a; Bass, 1993b; Glatz and van der Vusse, 1996; Weisinger, 1996).

Pathways of potential PPAR regulation have been elucidated whereby L-FABP facilitates rapid LC-PUFA uptake into nuclei (McIntosh et al., 2009) and directly interacts with PPARα (Hostetler et al., 2009; Hostetler et al., 2010; Tan et al., 2002). The PUFAmediated increase in the expression of PPARα-regulated LC-PUFA β-oxidative enzymes, L-FABPs, and PPARα itself is L-FABP dependent (Petrescu et al., 2013). However, it is not known if L-FABP contributes to specificity of PPARα activation with respect to n-3 vs. n-6 LC-PUFAs, or to specificity within the n-3 subfamily of PUFAs (e.g., EPA vs. DHA). Moreover, the molecular mechanisms underlying interactions between L-FABP, PPARα, and PUFAs have yet to be discerned.

4.3. Adipose storage and mobilization of PUFAs

Adipose tissue represents the primary reservoir of triacylglycerols from which free fatty acids are hydrolyzed and released into plasma (Spector, 2001), where they are transported as a physical complex highly but reversibly bound with albumin (Spector, 1986). As a result, the PUFA composition of adipose free fatty acids is very similar to that of plasma (Seidelin, 1995). Plasma free fatty acids contain approximately 17% n-6 PUFAs, of which 90–93% is LA (Edelstein, 1986). Only 1.2–2.5% of plasma free fatty acids are n-3 PUFAs, of which 59–77% is ALA. Free AA and DHA are present in very small amounts, accounting for less than 1% of all fatty acids in adipose tissue (Seidelin, 1995).

Regulation of PUFA storage in adipose tissue is not well understood. With regard to n-3 PUFAs, both slower uptake into adipose tissue (Summers et al., 2000) and higher mobilization (Raclot and Groscolas, 1994) in relation to other fatty acids have been observed. Dietary fatty acid availability, enzyme selectivity, rate of mobilization, and reuptake all likely affect the PUFA composition of adipose tissue (Raclot and Oudart, 1999).

4.4. PUFA transporters

Fatty acid binding proteins (FABPs) are small, cytosolic proteins (Hohoff, 1998; Ribarik Coe, 1998; Veerkamp, 1995) that influence fatty acid metabolism through facilitating uptake, transport, sequestration, and metabolic targeting of fatty acids from the plasma membrane to specific intracellular organelles (Ek et al., 1997; Murphy et al., 1999; Wolfrum et al., 2000) for β-oxidation, lipid synthesis, or signaling (Veerkamp et al., 1991; Weisinger, 1996). Nine isoforms of FABPs are currently known to be expressed throughout the body, including nervous tissue (Veerkamp and Zimmerman, 2001), with overlapping, but somewhat different substrate specificities (reviewed in (Storch and Corsico, 2008). Liver (L)-FABPs, in particular, have a high affinity for fatty acids (Gordon et al., 1983; Thompson et al., 1999), binding DHA and AA with comparable affinities at sub-micromolar

concentrations (Maatman et al., 1994; Richieri et al., 2000; Widstrom et al., 2001; Wolfrum et al., 2000). L-FABPs facilitate DHA, oleic (18:1n-9) and palmitic (16:0) acid (Reubsaet et al., 1990) transfer to the peroxisome. Consistent with the various roles of fatty acids, the functions of FABPs may be diverse and dependent on the FABP type and the cell in which they are present (Veerkamp and Zimmerman, 2001).

Alternatively, very long-chain n-3 PUFA intermediates may be transported between organelles in the unbound state or as their acyl CoA derivatives. Nonesterified fatty acids are able to desorb from lipid bilayers and diffuse through aqueous solution in the absence of a binding protein (Hamilton et al., 2001; Zucker, 2001). However, the rate of spontaneous membrane desorption slows greatly as chain length increases, and is made faster by unsaturation (Pownall, 2001). L-FABP has been shown to slow intermembrane diffusion (Zucker, 2001) but increase cytoplasmic diffusion (Luxon, 1996; Murphy, 1998) of fatty acids. A mathematical model has been formulated that predicts both processes (Weisiger and Zucker, 2002).

Within the last decade, studies have begun to assess the substrate specificity of the fatty acid transporters. Thus, CD36 selectively transports n-6 PUFAS LA and AA (Guo et al., 2013). Overexpression or deficiency of CD36 (Febbraio et al., 2002) and FABP are associated with steatosis (Miquilena-Colina et al., 2011), insulin deficiency (Luiken et al., 2002a) and resistance (Chabowski et al., 2004; Miquilena-Colina et al., 2011), hyperinsulinemia (Corpeleijn et al., 2008; Miquilena-Colina et al., 2011), and hyperlipidemia (Makinen et al., 2010; Meex et al., 2005). These data suggest that fatty acid transporters not only facilitate but also regulate cellular lipid utilization, and it has been proposed that fatty acid uptake is subject to short-term regulation by translocation of CD36 from intracellular storage sites to the plasma membrane (Glatz et al., 2002; Luiken et al., 2002b) while liver-type FABPc functions in long-term, ligand-induced regulation of gene expression by directly interacting with nuclear receptors (Glatz et al., 2002).

5. BRAIN PUFAS

5.1. Mechanisms of PUFA supply to the brain

Several mechanisms have been described for PUFA entry into the brain from the circulation (see Figure 2), derived from both rat (Lagarde, 2001; Smith and Nagura, 2001a; Thies et al., 1994) and human (Lagarde, 2001; Spector, 2001) studies. Albumin carries PUFAs in the non-esterified form, derived from adipose triacylglycerol stores or esterified in lysophosphatidylcholine, a partially hydrolyzed phosphatidylcholine retaining *sn*-1 or *sn*-2 fatty acids (Lagarde, 2001; Thies et al., 1994). Plasma lipoproteins are another transport medium for PUFAs esterified in triacylglycerols, phospholipids, and cholesteryl esters (Spector, 2001).

However, the molecular mechanisms by which fatty acids enter the brain are not agreed upon. Passage into the brain entails traversing first the luminal and abluminal membranes of the endothelial cells that comprise the blood brain barrier (Reese and Karnovsky, 1967), and then the plasma membrane of the neural cells. There is debate concerning whether the main

form of PUFA entering the brain is esterified or nonesterified; and the relative importance of energy-dependent protein facilitated transport *vs.* energy-independent passive diffusion.

5.1.1. PUFA esterification state during brain uptake—*In situ* brain perfusion in rodents (Hamilton et al., 2002; Hamilton, 2007; Ouellet et al., 2009; Smith and Nagura, 2001b) and *in vitro* studies in cell culture (Delton-Vandenbroucke et al., 1997; Moore et al., 1990; Moore et al., 1991) with radiolabelled fatty acids have demonstrated that nonesterified PUFAs, hydrophobic in nature, readily cross the blood brain barrier in a passive diffusion process that is not saturable and is regulated by albumin concentration. Rodent studies confirm that radiolabelled PUFAs enter the brain readily when injected into the plasma in the non-esterified form. Over 90% of radiolabelled arachidonic acid is cleared from plasma within 2 min, and brain phospholipids are almost completely pulse labeled at 1 min (DeGeorge et al., 1989; Nariai et al., 1991; Rapoport et al., 2001; Washizaki et al., 1994). Additional research suggests that lipoproteins containing esterified PUFAs are hydrolyzed at the rat brain endothelial cell surface by lipoprotein lipase (Brecher and Kuan, 1979; Purdon, 1997; Shirai et al., 1986), resulting in transfer of non-esterified fatty acids across the blood brain barrier. Incorporation rates of AA and DHA from the nonesterified plasma pool into rat brain phospholipids are rapid (approximately 5pmol/g brain/s, for AA) and closely approximate independent measures of their respective brain consumption rates (Chen et al., 2008a). Thus, although nonesterified PUFAs in serum amount to approximately 17% of n-6 PUFA and 10-fold less of n-3 PUFA (Edelstein, 1986), they likely serve as a major source of PUFAs for the brain. Taken together, these findings suggest that despite the low level in plasma, the nonesterified form is a primary source of brain PUFAs, derived from both albumin-PUFA complexes and PUFAs carried in lipoproteins.

However, evidence from one research group supports uptake of esterified PUFAs as a significant mode of transfer across the blood-brain barrier. DHA esterified to lysophophatidylcholine was taken up more efficiently than the non-esterified forms in brain-capillary endothelial cell and astrocyte cell co-cultures (Bernoud et al., 1999; Lagarde, 2001) and into brains of 20 day-old rats (Lagarde, 2001), but not into liver, heart, or kidney (Thies et al., 1994). This group found that the percentage of labelled DHA in rat brain lipids after [^{3}H]DHA-lysophophatidylcholine infusion was approximately 10-fold higher than that of unesterified DHA (Thies et al., 1994), and that lysophophatidylcholine was primarily found in association with albumin, which they propose as an effective mechanism of delivering PUFA to brain (Croset et al., 2000).

Preliminary evidence that lysophosphatidylcholine may play a significant role in transport has been strengthened with the recent discovery that Mfsd2a, of the major facilitator superfamily and previously an orphan transporter, functions as a major, sodium-dependent symporter of lysophosphatidylcholine-DHA into brain of immature mice, and Mfsd2a-knockout mice exhibit reduced brain DHA levels (Nguyen et al., 2014). Studies using the pulse-labeling method (Robinson et al., 1992) remain to be done in adult animals to clarify this mechanism. In both rodents and humans, about 55% of DHA is esterified to lysophosphatidylcholine, with 45% in the non-esterified form (Lagarde, 2001).

An additional hypothesis is that lipoproteins themselves, containing the esterified PUFAs, are taken up by endothelium, and the resultant phospholipids are hydrolyzed intracellularly. Supporting evidence includes the presence of lipoprotein lipase and acid lipase activity in cerebral microvasculature from rabbit brain (Brecher and Kuan, 1979). and LDL receptors in the bovine cerebral vascular endothelium (de Vries, 1993; Dehouck et al., 1994; Dehouck et al., 1997; Herz and Bock, 2002; Lucarelli et al., 1997); the ability of the HDL_3 subfraction to bind to bovine brain capillary endothelial cells (Martin-Nizard et al., 1989); and, in dogs and humans, the presence of apolipoproteins as well as LDL and HDL particles that have crossed the blood brain barrier into cerebrospinal fluid (Hesse et al., 2000; Pitas et al., 1987), although their presence may be due to ultrafiltration through the choroid plexus (Rapoport and Pettigrew, 1979). Furthermore, LDL can undergo transcytosis through rat and bovine brain capillary endothelial cells (Candela et al., 2008; Dehouck et al., 1997). Similarly, in rats, intravenously injected triacylglyerol-rich lipoproteins and lipid emulsions can be directly taken up *in vivo* by tissues as intact particles with little lipolysis (Hultin et al., 1995). However, the biological relevance of these phenomena to brain PUFA homeostasis is unclear, as studies using knock-out mice have found that neither LDL (Chen et al., 2008b) nor VLDL (Rahman et al., 2010) receptors are necessary for regulating brain PUFA concentrations. One possibility is that the receptors are critical for transport and function of the capillaries themselves, but not necessarily for neurons or glia on the abluminal surface. Capillary isolation studies are in order (Williams et al., 1997).

5.1.2. Passive diffusion or protein-facilitated transfer?—Current models for brain uptake of non-esterified fatty acids postulate passive diffusion using a “flip-flop” mechanism, fatty acid transport protein-facilitated movement, or a combination of both (Chen et al., 2008a). A rapid reversible flip-flop diffusion mechanism is consistent with known biophysical properties of LC-PUFAs in biomembranes (Hamilton, 2007; Hamilton and Brunaldi, 2007). Others have challenged this model, however, asserting that in biological membranes, flip-flop is not rapid but rather is a rate-limiting step that may only be overcome with the assistance of proteinmediated PUFA transport (Cupp et al., 2004; Kampf et al., 2006).

The facilitated transfer hypothesis is given face validity by the existence of multiple putative lipid transporter proteins including isoforms of the integral membrane protein FATP (DiRusso et al., 2005; Jia et al., 2007; Melton et al., 2011), the transmembrane protein CD36 (Bastie et al., 2004; Drover et al., 2008; Ibrahimi et al., 1996; Nickerson et al., 2009), and the peripheral membrane fatty acid binding protein (FABPpm) (Luiken et al., 1999; Potter et al., 1987; Schwieterman et al., 1988; Sorrentino et al., 1988; Sorrentino et al., 1991; Stremmel et al., 1985a; Stremmel et al., 1985b; Stremmel et al., 1986; Stremmel, 1988a; Turcotte et al., 2000). In this model, fatty acid transporters are believed to attach PUFA molecules on the luminal face of cerebral endothelial cells and diffuse across both the endothelial and the neuronal cell membranes (Abumrad et al., 1998). However, FATP do not act as simple transporters; rather, through acyl-CoA synthetase activity, they indirectly drive PUFA uptake through “quenching” (Chen and Bazinet, 2014) the fatty acids by esterifying them with CoA, forming a non-diffusible fatty acid compound that is trapped within the cell (Jia et al., 2007), a possible rate-limiting step for PUFA incorporation into brain (Black and

DiRusso, 2003). Similarly, CD36 proteins have been demonstrated in HEK 293 cell lines not to physically transport PUFAs but rather to promote uptake by upregulating intracellular esterification of PUFAs to triacylglycerols (Xu et al., 2013). CD36-null mice evince learning deficits but do not differ in brain AA or DHA concentrations from wildLiu p. 30 type mice (Song et al., 2010), and thus CD36 likely does not play a major role in maintaining brain PUFA stores. Once inside the cell, the LCPUFA binds to a FABP molecule on the inner leaflet of the plasma membrane for intracellular transport. In human brain, this transport process is characterized by differential permeability with respect to the apical-basolateral direction of fatty acid movement (Mitchell et al., 2011), and selectivity, as essential PUFAs enter the brain while cholesterol and nonessential fatty acids do not (Edmond, 2001) (but see (Pardridge and Mietus, 1980).

FABPs in the brain exhibit distinct, isoform-specific temporal distributions (Storch and Corsico, 2008; Veerkamp and Zimmerman, 2001). Brain (B)-FABP and epidermal (E)-FABP (also known as keratinocyte [K]-FABP) are mainly expressed in developing brain (Owada, 2008). B-FABP preferentially binds n-3 PUFAs, especially DHA (Balendiran et al., 2000; Hanhoff et al., 2002; Xu et al., 1996), and its expression is directly correlated with DHA utilization. B-FABP null mice incorporate decreased DHA and increased AA into phospholipids (Owada, 2008). E-FABP is expressed mainly in the embryo and may also play a role in regeneration of neurons after injury (De Leon et al., 1996; Owada, 2008). During adulthood, heart (H)-FABP is also expressed in brain, where its concentration is more than 10-fold that of B-FABP, suggesting that it helps to maintain the differentiation status of adult brain cells (Owada, 2008). The efficacy of LCPUFA absorption into brain may be affected by genetic polymorphisms and epigenetic changes affecting expression patterns of transporters. For example, expression of BFABP is increased in schizophrenia (Watanabe et al., 2007) and Down syndrome (Cheon et al., 2003; Sanchez-Font et al., 2003), whereas H-FABP brain protein levels are lower in both Down syndrome and Alzheimer's disease (Cheon et al., 2003).

5.1.3. Endogenous fatty acid synthesis by the brain—While it is generally accepted that the brain obtains essential PUFAs from blood, it may also produce LC-PUFAs from precursors (Berg JM, 2002). Endothelial cells comprising the blood-brain barrier accomplish the initial elongation and desaturation steps (Moore et al., 1990), and astrocytes may also produce DHA and AA (Moore et al., 1991). Developing rat brain is capable of converting ALA to DHA (Dhopeshwarkar and Subramanian, 1976), and can also take up, convert, and selectively esterify PUFAs into phospholipids (Green and Yavin, 1993). However, radiolabelled ALA entering the brain is almost completely metabolized to its β-oxidation products, with less than 0.2% transformed to DHA (Demar et al., 2005). Even under conditions of low dietary AA, less than 1% of the LA precursor is transformed to AA in adult rat brain (DeMar et al., 2006). Thus, even when the diet is PUFA deficient, endogenous brain production is a minor contributor compared to the liver, and is not significantly upregulated in response to deficiency states.

5.2.1. Maintenance of PUFA composition in the brain

Plasma PUFAs equilibrate to about 90% of maximal brain uptake within 15 min (Rapoport, 1999), and the higher the degree of unsaturation, the more rapid the uptake (Lagarde, 2001). In contrast, brain DHA loss is very slow: in rat pups on an n-3 PUFA adequate diet, the half-life of DHA in total brain phospholipids is 33 days (Demar et al., 2004). Moreover, the brain retains DHA longer under conditions of deficiency (Gazzah et al., 1995). For example, in rat pups deprived of dietary n−3 PUFA for 15 weeks, brain DHA half-life increases twofold (Demar et al., 2004), and the brain retains its DHA stores at the expense of other organs for long periods of deprivation (Bourre et al., 1992). An exception is that in reproducing female rats, brain DHA content falls by 20% during gestation and nursing (Levant et al., 2006), an observation that may have relevance for postpartum depression in humans. In rats fed a n-3 deficient diet for multiple generations (Contreras et al., 2000), and in nursing dams (Levant et al., 2006), the lost DHA content is replaced by 22:5n-6 DPA. In contrast to DHA, recent rodent studies of the kinetics of EPA metabolism find that the brain maintains low levels of EPA through extremely rapid rates of β-oxidation (Chen and Bazinet, 2014; Igarashi et al., 2013). Dietary PUFA supplementation can reverse reductions in PUFA concentrations in brain and peripheral organs caused by dietary deprivation. Deprived rats subsequently fed an n-3 sufficient diet were able to recover DHA levels in the brain after three weeks; however, recovery half-life was considerably shorter for non-neural tissues and blood (Ikemoto et al., 2001; Moriguchi et al., 2001). The slower recovery of DHA by the brain has been attributed to the small contributions (2–4%) of plasma PUFAs to the net quantity that is re-esterified (Shafrir et al., 1965; Wosilait and Soler-Argilaga, 1975), or to slow transfer of DHA synthesized in astrocytes to neurons (Moore, 2001). However, kinetic modeling studies with radiolabelled fatty acids in awake adult rats find that the turnover of 3–5% of AA and 2–8% of non-esterified DHA entering the esterified brain pool each day (Rapoport, 2001; Rapoport, 1999; Rapoport et al., 2001) is adequate to counterbalance metabolic loss.

5.2.2. Effects of PUFA balance on brain

One useful metric of PUFA status is the relative proportion of n-3 and n-6 PUFAs, which has been reported to affect monoaminergic transmission (Chalon, 2006b) and has ramifications for major mood disorders (Adams et al., 1996; De Vriese et al., 2003; Maes et al., 1996; Maes et al., 1999a; Mamalakis et al., 2004), functional improvement in psychotic disorders (Amminger et al., 2010), and cognitive decline (Heude et al., 2003). Low n-3 relative to n-6 PUFA status also has been implicated in risk of suicide attempts (Huan et al., 2004; Sublette et al., 2006) and suicide (Lewis et al., 2011). PUFA imbalance also may underlie the observed relationship of cholesterollowering treatments with higher rates of non-cardiac illness mortality due to suicide and other types of violent death (Muldoon et al., 1990; Muldoon et al., 2001), e.g. gemfibrozil (Nyalala et al., 2008) increases the lipid proportion of AA.

The factors governing the maintenance of PUFA balance in the brain are not completely understood. Turnover (recycling) is one nexus of regulation (Chen et al., 2008a), controlled to some extent by PUFA species-specific PLA_2 isoforms: for example, cytosolic calcium-independent group IVA $cPLA_2$ for AA (Clark et al., 1991) and calcium-independent group VIA $iPLA_2$ for DHA (Green et al., 2008; Strokin et al., 2003), as well as acyl-CoA

synthetases, for example acyl-CoA synthetase-4 for AA (Shimshoni et al., 2011; Soupene and Kuypers, 2008). H-FABP expression is also necessary to maintain the n-6:n-3 PUFA balance in adult brain cells, and lower H-FABP expression reduces the incorporation of AA into brain phospholipids (Murphy et al., 2005).

Studies of major depression suggest that the balance of individual n-3 subspecies is also important. In a meta-analyses of PUFA status in depression, both lower DHA and EPA levels distinguished depressed from healthy groups (Lin et al., 2010); however, meta-analyses of clinical trials in depression find that supplements containing higher proportions of EPA are more effective than those containing higher amounts of DHA (Lin et al., 2012; Martins, 2009; Martins et al., 2012; Ross et al., 2007). Reasons for this are unknown, although there are a number of non-brain contexts in which EPA and DHA have different functionality. Well-studied examples are that EPA competes with AA, its 20-carbon n-6 congener, for binding to cPLA2α and to COX-1 (Smith, 2005); and that EPA is a much stronger activator of PPARα than DHA (Jump, 2008; Jump et al., 2008b). Conversely, DHA has more powerful effects than EPA on lipid raft structure (Williams et al., 2012). Experimental n-3 PUFA deficiency results in compensatory elevations of DPAn-6 (22:5n-6) derived from liver elongation of AA (Kim et al., 2011; Moriguchi, 2004), which displays very different lipid matrix properties from DHA, although it contains only 1 fewer double bond (Eldho et al., 2003). However, to our knowledge, significant elevations of plasma DPAn-6 have not been demonstrated in presumed severe clinical n-3 PUFA deficiency.

5.3. PUFA roles in brain function

Development of novel, lipid-based neuropsychiatric treatments will require an indepth understanding of PUFA actions in the brain. Preclinical studies in cell cultures and rodent models have elucidated many brain PUFA functions including participation in neurotransmission, neuroinflammation, neuroprotection, and energy maintenance, discussed below. Recently, the development of fatty acid radiotracers for use in positron emission tomography (PET) has made possible the *in vivo* study of PUFA uptake into human brain. [1-^{11}C]AA has been used to characterize unesterified AA incorporation into brain in healthy adults (Thambisetty et al., 2012), in aging (Esposito et al., 2007b; Giovacchini et al., 2002; Giovacchini et al., 2004; Rapoport et al., 2011; Umhau et al., 2009), and in patients with Alzheimer's disease (Esposito et al., 2008); and during functional or pharmacological dopaminergic D2 receptor activation (Esposito et al., 2007a; Thambisetty et al., 2012), while [1-^{11}C]DHA has been used to study baseline brain DHA consumption and chronic alcoholism (Umhau et al., 2013). Another new radiotracer, [^{18}F]-fluoroarachidonic acid (Pichika et al., 2012), is now under development.

5.3.1. PUFAs and signaling pathways in the brain—PUFAs can modulate many signal transduction mechanisms in neuronal membranes and the synapse. As serotonin (5-HT_1 and 5-HT_4), beta-adrenergic and dopamine (D_1 and D_2) receptors are all coupled to the cAMP messenger system, PUFAs can influence them by increasing adenylate cyclase (Murphy, 1985; Nicolas et al., 1991) and protein kinase A (Speizer et al., 1991) activity. Animal studies, in piglets (de la Presa Owens and Innis, 1999) and in two generations of rats (Zimmer et al., 1999; Zimmer et al., 2000b) fed n-3 PUFA deficient diets identify many

effects on dopaminergic systems, including lower levels of dopamine (de la Presa Owens and Innis, 1999; Zimmer et al., 2000c), D_2 receptors, D_2 receptor mRNA and dopaminergic presynaptic vesicles (Zimmer et al., 2000c), and increased breakdown of dopamine (Zimmer et al., 1998), in the prefrontal cortex. Experimental n-3 PUFA deficiency in rat dams shortly after conception also results in offspring with decreased tyrosine hydroxylase (Kuperstein et al., 2008), the rate-limiting enzyme in dopamine synthesis; fewer detectable dopaminergic neurons in the substantia nigra and ventral tegmentum (Ahmad et al., 2008); and elevated postnatal expression of dopamine receptor genes in rat pups (Kuperstein et al., 2005). After two generations of n-3 PUFA deficiency, rats also exhibit higher dopamine levels, D_2 receptor mRNA, D_2 receptors, and less release and breakdown of dopamine in the nucleus accumbens (Zimmer et al., 2000a). Conversely, two generations of a high-n-3 PUFA diet increases dopamine levels in rat prefrontal cortex by 40% and elevates D_2 receptor binding, while lowering monoamine oxidase B activity in prefrontal cortex and D_2 receptor binding in striatum (Chalon et al., 1998). PUFA associations with dopamine also have been implicated in clinical depression (Sublette et al., 2014). Less has been reported concerning dietary PUFA effects on serotonin (5-HT), although, compared with normally fed animals, rats with low brain DHA had decreased 5-HT levels and turnover in frontal cortex (nulliparous females) and higher density of hippocampal 5-HT_{1A} receptors (parous dams) (Levant et al., 2008). Also, in 2-month old male rats, stimulated 5-HT release in the hippocampus was lower in rats fed a n-3 PUFA deficient diet for two generations, and the ability of diet alteration to reverse this deficiency decreased over time after parturition (Chalon, 2006a). However, in adult male mice, n-3 PUFA supplementation was effective in reversing 5-HT levels that had declined by 40–65% as a result of unpredictable chronic mild stress (Vancassel et al., 2008). On the other hand, in one study comparing high saturated fat, high n-3 PUFA, and high n-6 PUFA diets, 5-HT_{2A} receptor and 5-HT transporter binding were most strongly affected by the n-6 PUFA diet (Dubois et al., 2006).

PUFAs also can interact with the phosphoinositide signaling pathway by exerting effects on phospholipase C (Irvine et al., 1979) and protein kinase C (McPhail et al., 1984a; McPhail et al., 1984b), both of which are involved in 5-HT_2 and alpha-1 adrenergic mediated signal transduction.

Neurotransmitters affect PUFA turnover, as PLA_2 is activated by multiple receptor types--dopamine D_2 (Vial and Piomelli, 1995), serotonin 5-HT_2 (Berg et al., 1996), glutamate (Tence et al., 1995), and muscarinic acetylcholine (Jones et al., 1996)--to liberate fatty acids from the *sn*-2 position of phospholipids. In turn, PUFAs also regulate the activity, mRNA expression, and protein levels of multiple PLA_2 isoforms (Downes and Currie, 1998; Lister et al., 1988; Rao et al., 2007a).

Fatty acids that are not recycled back into phospholipids can be metabolized through several pathways, e.g. cyclooxygenase (COX)-2 (O'Banion, 1999) acts on AA, EPA and DHA (Serhan et al., 2002) to produce prostanoids (prostaglandins [PGE] and thromboxanes) (Chang and Karin, 2001; Kozak et al., 2001), while lipoxygenases produce leukotrienes and lipoxins. PGEs occur in 3 families which have different effects through interactions with specific signaling systems: the PGE-2 family transduces signals via a G_s protein, elevating cAMP levels, whereas the PGE-3 family uses a G_i protein, lowering cAMP, and the PGE-1

family acts through a phosphoinositide signaling system (Smith, 1992). Eicosanoids, 20-carbon n-6 compounds, and docosanoids, 22-carbon n-3 compounds that include resolvins or neuroprotectins, can have opposing effects on signal transduction and inflammatory processes (Calder, 2006b; Piomelli, 1994).

Release of neurotransmitters from synaptic vesicles by activation of Ca2+/calmodulin dependent protein kinase is affected by PUFAs (Piomelli et al., 1989), and Ca-ATPase in neuronal membranes is inhibited by DHA and EPA (Kearns and Haag, 2002).

5.3.2. PUFAs and neuroinflammation—PUFAs regulate inflammation largely through the actions of their bioactive eicosanoid and docosanoid metabolites, which play distinct roles and have complex interactions in the development and resolution of acute inflammation (Calder and Grimble, 2002; Stables and Gilroy, 2011) (see Figure 3). In contrast to the generally pro-inflammatory n-6 derived eicosanoids, the DHA-derived docosanoids display primarily anti-inflammatory effects, including in brain (Orr et al., 2013). For example, neuroprotectin D1 (NPD1) downregulates peptide-induced proinflammatory cytokine expression in microglia (Bazan et al., 2005; Bazan, 2009; Connor et al., 2007), and resolvins block the production of NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) and pro-inflammatory cytokines by microglial cells (Marcheselli et al., 2003).

As in peripheral systems, the balance between n-6 and n-3 PUFAs thus can have profound effects on neuroinflammation. For example, as n-3 and n-6 LC-PUFAs compete for membrane insertion, an n-3 PUFA-enriched diet increases production of anti-inflammatory docosanoids and decreases the n-6 content of glial cell membranes, resulting in less substrate available for AA-derived eicosanoid synthesis (Calder, 2006a). Some examples with clinical relevance include rodent models of metabolic and behavioral responses to traumatic brain injury, in which n-3 PUFA deficiency states worsened post-injury anxiety-like behavior (Agrawal et al., 2014) and sensorimotor impairments (Russell et al., 2013), and resulted in lower levels of anxiolytic neuropeptide Y1 receptor (Agrawal et al., 2014) and mRNA expression of tissue inhibitor of matrix metalloproteinase-1 (Timp1) (Russell et al., 2013). Supplementation with n-3 PUFAs in the diet prior to experimental injury mitigated the usual sequelae of abnormal levels of brain-derived neurotrophic factor (BDNF), synapsin I, and cAMP responsive element-binding protein (CREB) (Wu et al., 2004), as well as axonal injury, apoptosis (Mills et al., 2011), and cognitive impairments (Mills et al., 2011; Wu et al., 2004). Moreover, in a mouse model, even after experimental brain injury, an inhibitor of fatty acid amide hydrolase (FAAH) reduced breakdown of the PUFA metabolite anandamide, and thereby mitigated fine motor and working memory impairments and anxiety-like behaviors, concomitantly reducing neurodegeneration and amyloid precursor protein, and upregulating stress-responsive growth factors and heat shock proteins (Tchantchou et al., 2014).

5.3.3. PUFAs as regulators of brain energy—DHA also has been identified as an important regulator of brain energy metabolism, having effects on both glucose uptake and on the density of glucose transporter-1 (GLUT1) in endothelial cell cultures (Pifferi et al., 2007) and in cerebral cortex from rat brain (Pifferi et al., 2005). Neuroimaging in humans

with [^{18}F]-fluoro-2-deoxyglucose positron emission tomography (FDG-PET) has identified correlations between plasma PUFA levels and cerebral metabolic rates for glucose (rCMRglu) in specific brain regions (Sublette et al., 2009).

5.3.4. PUFAs and neuroprotection—The benefits of n-3 LC-PUFAs to neuropsychiatric health are likely afforded, in part, by their neuroprotective properties. DHA and its metabolite NPD1 alter the expression of pro- and anti-apoptotic genes, including Bcl-2, Akt, and Bfl-1 (Akbar and Kim, 2002; Akbar et al., 2005; Bazan, 2007), positively affecting neuronal survival. Resolvins, too, protect the brain from ischemia (Marcheselli et al., 2003). Dietary DHA also confers neuroprotection by specifically reducing β-amyloid in an mouse model of Alzheimer's disease (Lim et al., 2005a) and in cytokine-stressed human neural cells (Lukiw et al., 2005), while in an *in vivo* human study, elevated AA brain uptake was seen with PET, in patients with Alzheimer's disease compared to healthy volunteers (Esposito et al., 2007a). Conversely, *in vivo* DHA depletion has been shown to result in decreased brain-derived neurotrophic factor (BDNF) in rodents (Rao et al., 2007c) and increased neuronal cell death in cell cultures (Akbar et al., 2005).

5.4. Inferring PUFA mechanisms of action from medication effects

Rapoport et al. have shown that mood stabilizers and some atypical antipsychotics FDA-approved for treating bipolar disorder have direct or indirect convergent effects on the AA cascade in rat brain, such as decreasing AA turnover in phospholipids or expression of AA-selective cPLA2 IV-A or COX-2 or inhibiting AAselective acyl-CoA synthetase-4 (Shimshoni et al., 2011). These medications include lithium (Basselin et al., 2003; Basselin et al., 2005; Basselin et al., 2006; Basselin et al., 2007), carbamazepine (Bazinet et al., 2006a), valproic acid (Bazinet et al., 2006b), clozapine (Modi et al., 2013), lamotrigine (Lee et al., 2008), and olanzapine (Cheon et al., 2011). Conversely, the medication topiramate, which did not have significant benefit in clinical trials in bipolar disorder (Delbello et al., 2005), also had no effects on rat brain AA metabolism (Lee et al., 2005). Additionally, two antidepressants implicated in triggering manic episodes, fluoxetine (Lee et al., 2006) and imipramine (Lee et al., 2010), increased AA turnover (Lee et al., 2006; Lee et al., 2010) and upregulated $cPLA_2$ (Lee et al., 2010), while the more dopaminergic antidepressant bupropion had no effects on AA turnover (Lee et al., 2010).

Taken together, these results suggest that bipolar mood instability may be related to dysregulation of the AA cascade.

5.5. Relevance of peripheral PUFA biomarker data

Interpreting the results of studies using peripheral PUFAs as biomarkers is complicated by several factors: 1) *Esterification*. Few human studies analyze levels of nonesterified PUFAs. However, non-esterified PUFAs readily cross the blood brain barrier and their plasma concentrations are tied closely to brain consumption rates (Chen et al., 2008a), although the relationship between plasma and brain DHA levels may be nonlinear (Rapoport, 2013). In one study in bipolar disorder (Sublette et al., 2007), manic symptoms correlated with nonesterified but not esterified plasma PUFA concentrations. 2) *Tissue source* (adipose, total plasma, plasma lipid subfractions, platelets, erythrocytes). It has been assumed by some that

erythrocyte PUFA concentrations give the best indication of long-term PUFA status, given the longevity of red blood cells. However, the membrane PUFA composition of erythrocytes is not static throughout their lifetime, but rather experiences turnover as in other tissues. In fact, PUFA constituents of erythrocytes exhibit diet-related changes within 24 hours (Hodson et al., 2008), similar to plasma and platelet time courses (Skeaff et al., 2006). 3) *Lipoprotein status*. In total plasma PUFAs, percentages of n-3 PUFAs may be strongly influenced by the relative amounts of different lipoproteins (Hodson et al., 2008). Different types of lipoproteins carry characteristic proportions of triacylglycerols, cholesteryl esters, and phospholipids, e.g., HDL contains the largest percentages of LCPUFAs. These lipids in turn exhibit individually distinct PUFA profiles. Therefore, individual differences in lipidemia may confound the study of total plasma PUFAs, and the use of phospholipid fractions may mitigate this problem. 4) *PUFA species*. Quantification of levels of all PUFAs that are separable by chromatography provides a comprehensive picture but incurs loss of statistical power for group comparisons. In contrast, clinical approaches which focus *a priori* on a few well-characterized PUFAs (frequently DHA, AA, EPA) retain more statistical power but run the risk of oversimplification and overlooking the contribution of less abundant PUFA species or their metabolites (Yuan et al., 2013). Moreover, it is unclear whether absolute levels or proportions of total plasma PUFA are more physiologically relevant.

6. CONCLUSIONS

From the perspective of precision medicine (National Research Council, 2011), patients with low n-3 PUFA levels relative to n-6 PUFA may represent a biological subgroup that is at greater risk for psychiatric illness. Suboptimal n-3 PUFA intake may also predispose such patients to other medical comorbidities, e.g. depression and cardiac illness are highly comorbid (Musselman et al., 1998), and low n-3 PUFA levels have been implicated in both conditions.

The majority of studies concerning PUFAs in neuropsychiatric illness have focused on brain development and mood, psychotic and cognitive disorders. Less is known about PUFA status in anxiety disorders, substance abuse, or personality disorders. Surprisingly little is known about the effects of low essential LC-PUFA intake in context of eating disorders, which in their most severe forms carry a high rate of major depression and suicide risk.

Given that low n-3 PUFA and excess n-6 PUFA intake are widespread in many countries, it is likely that the occurrence of psychiatric illness does not depend solely on dietary imbalance. We hypothesize that low n-3 PUFA intake is likely to have the greatest impact if combined with metabolic or genetic abnormalities affecting PUFA absorption, transport, interconversion, membrane turnover, or catabolism. A wellstudied instance is the genetically controlled expression of FADS enzymes affecting the fatty acid composition of serum phospholipids in times of suboptimal LC-PUFA dietary intake (Al-Hilal et al., 2013; Glaser et al., 2010; Nwankwo et al., 2003; Schaeffer et al., 2006a) that may lead to individual differences in dietary requirements (Koletzko et al., 2008) and contribute to psychiatric illness including schizophrenia (Liu et al., 2009a) and bipolar disorder (Liu and McNamara, 2011a). Additionally, low levels of n-3 PUFA may contribute to psychiatric illness by

interacting with other types of external environmental stress or genomic factors involving stress response systems. For example, in rodents, PUFA deficiency plus environmental stress is more likely to produce anxiety-like behaviors than either alone (Bandaru et al., 2010; Harauma and Moriguchi, 2011; Liu et al., 2013; Mathieu et al., 2008; Mathieu et al., 2011). Therefore, there is a need for studies to assess environmental, genetic, and epigenetic influences on PUFA metabolism and their impact on neuroinflammation in the pathogenesis of psychiatric disorders.

Acknowledgments

Funding

Work by Dr. Rapoport was supported entirely by the Intramural Program of the National Institute on Aging. Work by Dr. Sublette was supported in part by NIMH MH079033.

Dr. Mann received royalties from Research Foundation for Mental Hygiene for commercial use of the C-SSRS and stock options in Qualitas Health, a startup company developing a polyunsaturated fatty acid nutritional supplement. Dr. Sublette received a grant of nutritional supplements from Unicity International for an unrelated study.

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Review Highlights

- Essential polyunsaturated fatty acids (PUFAs) are integral for brain functioning
- Absorption, delivery, transport, or metabolic problems can influence PUFA levels
- Understanding mechanisms of PUFA supply to the brain is relevant for neuroscientists

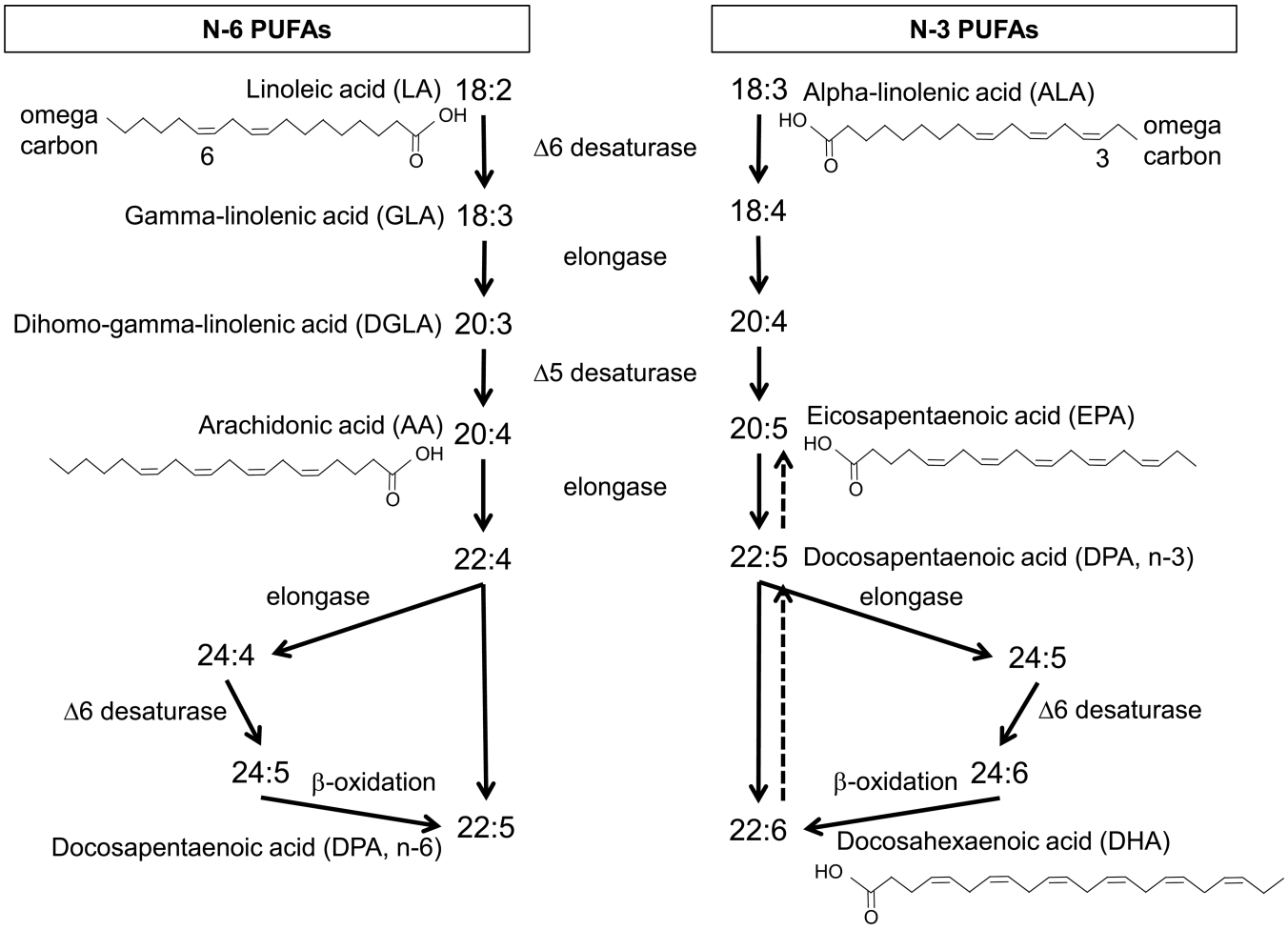

Figure 1. Long-chain polyunsaturated fatty acid (PUFA) synthesis from parent essential fatty acids

Long-chain (LC)-PUFAs not acquired directly through diet can be synthesized through desaturation, elongation, and β-oxidation steps (solid arrows) from shorter-chain precursors. N-6 and n-3 PUFAs compete for Δ5 and Δ6 desaturases. Small amounts of apparent retroconversion from DHA to DPA and EPA also have been reported (Plourde et al., 2011) (dashed arrows).

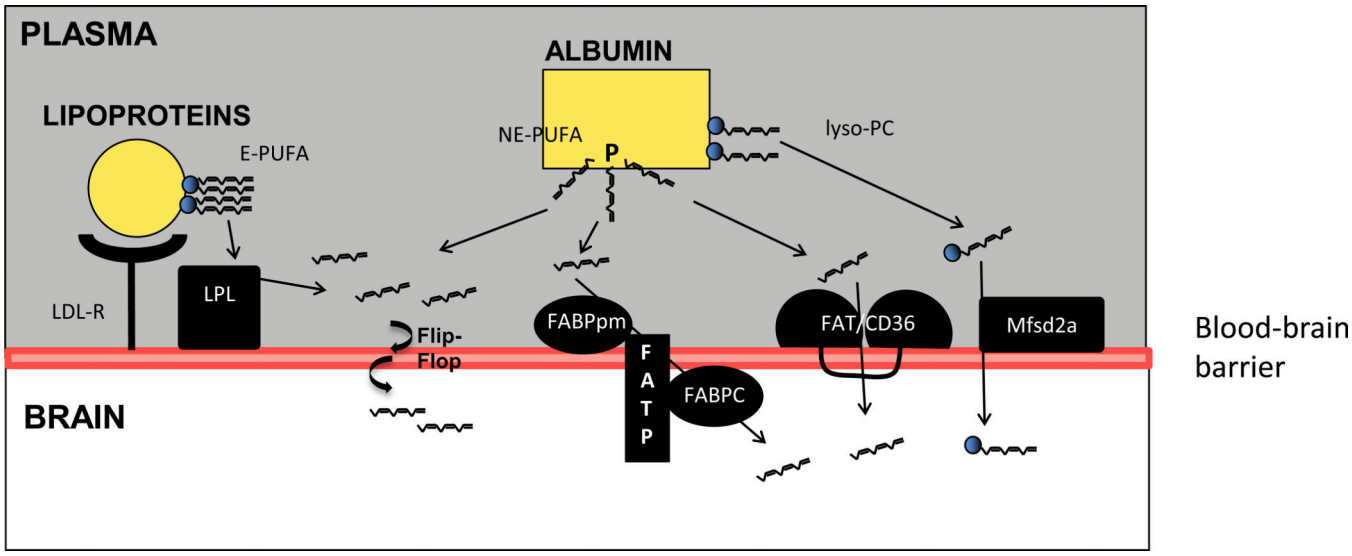

Figure 2. Proposed mechanisms of Polyunsaturated Fatty Acid Passage Across the Blood-Brain Barrier

Polyunsaturated fatty acids (PUFA) are primarily delivered to the brain capillary bed via lipoproteins, in esterified form (E-PUFA); or via albumin, esterified to lysophosphatidylcholine (lyso-PC) or unesterified (NE-PUFA) in a rapidly dissociable lipid-protein complex. Evidence exists for several entry mechanisms into endothelial cells of blood brain barrier and into brain: LDL receptors (LDL-R) bind to the lipoprotein, and lipoprotein lipases (LPL), present on the luminal surface of cerebral endothelial cells, liberate PUFA by hydrolysis of ester bonds. Both NE- and E-PUFA can cross the blood-brain barrier by passive diffusion through a flip-flop mechanism. Fatty acid binding proteins on the external (FABPpm) and internal (FABPc) plasma leaflets assist PUFA transport, which may occur via integral membrane proteins, fatty acid transport protein (FATP) or fatty acid translocases (FAT/CD36). FATP indirectly drives fatty acid uptake by esterifing PUFA to CoA inside the cell, effectively trapping the nondiffusible acyl-CoA-PUFA compound. DHA-containing lysoPC molecules are transported via major facilitator molecule, Mfsd2a. *Abbreviations:* E-PUFA = esterified polyunsaturated fatty acids; FABP = fatty acid binding protein; FABPpm = peripheral membrane fatty acid binding protein; FABPc = cytoplasmic (intracellular) fatty acid binding protein FAT/CD36 = fatty acid translocase/ cluster of differentiation 36; FATP = fatty acid transport protein; LDL-R = low density lipoprotein receptor; LPL = lipoprotein lipase; lyso-PC = lysophosphatidylcholine; NE-PUFA = non-esterified fatty acids.

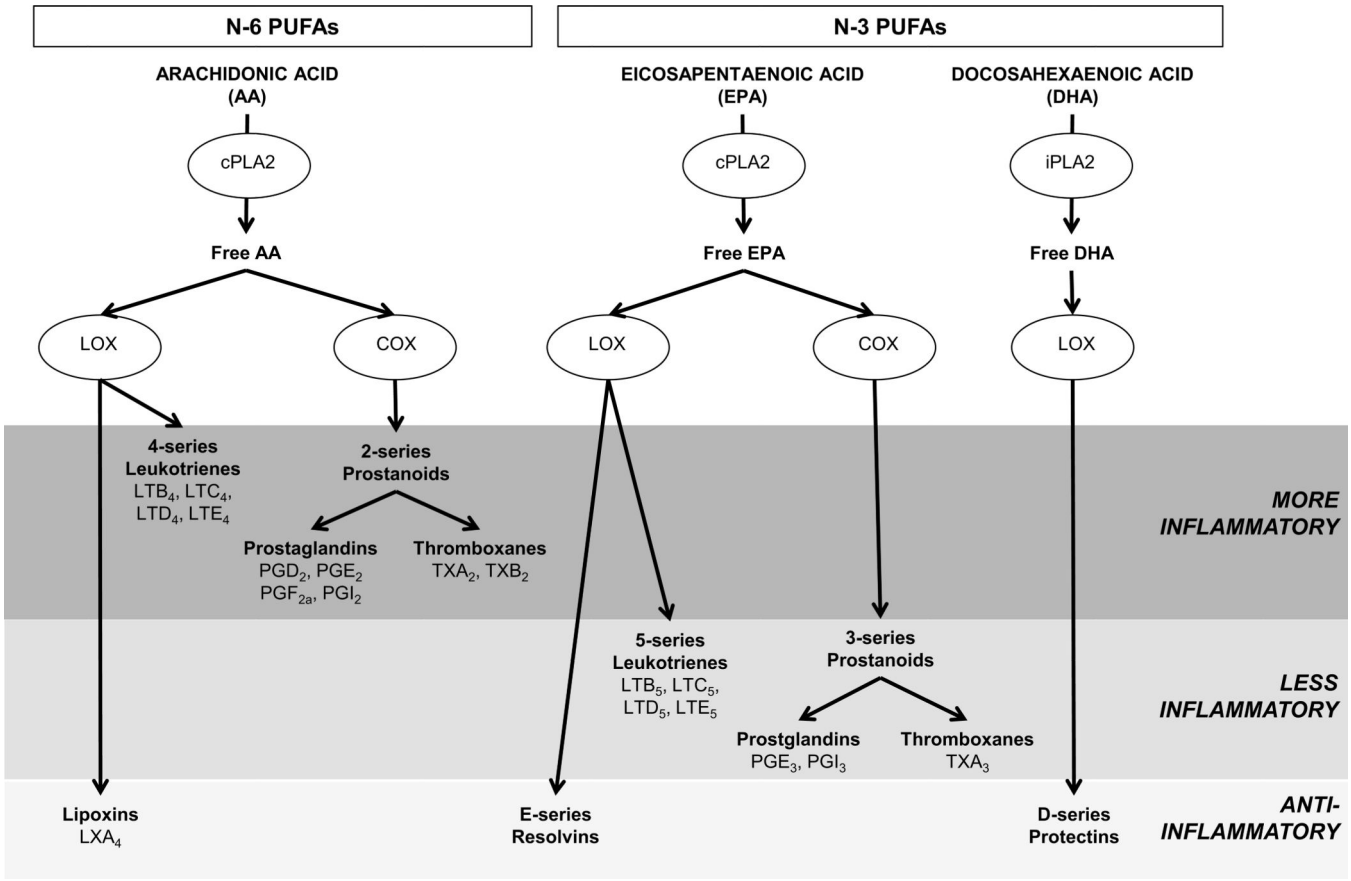

Figure 3. Inflammatory status of polyunsaturated fatty acid (PUFA) metabolites

PUFAs mediate inflammatory responses through the actions of bioactive eicosanoid and docosanoid metabolites. Eicosanoids derived from the n-6 PUFA family are generally pro-inflammatory, whereas the eicosanoids and docosanoids derived from the n-3 PUFA family are less pro-inflammatory or have anti-inflammatory effects, as do n-3 derived lipoxins. *Abbreviations:* COX = cyclooxygenase; cPLA2 = cytosolic phospholipase A2; iPLA2 = Ca2+-independent phospholipase A2; LOX = lipoxygenase; PLA2 = phospholipase A2; PUFA = polyunsaturated fatty acids.