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Review

Pathways of polyunsaturated fatty acid utilization: Implications for brain function in neuropsychiatric health and disease ☆

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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.

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1. Introduction

Lipids, which compose cell membranes, occur in very high concentrations throughout the central nervous system (Jumpsen and Clandinin, 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;

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