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Review

Food for thought: Dietary changes in essential fatty acid ratios and the increase in autism spectrum disorders

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ABSTRACT

The last decades have shown a spectacular and partially unexplained rise in the prevalence of autism spectrum disorders (ASD). This rise in ASD seems to parallel changes in the dietary composition of fatty acids. This change is marked by the replacement of cholesterol by omega-6 (n-6) fatty acids in many of our food products, resulting in a drastically increased ratio of omega-6/omega-3 (n-6/n-3). In this context, we review the available knowledge on the putative role of fatty acids in neurodevelopment and describe how disturbances in n-6/n-3 ratios may contribute to the emergence of ASDs. Both clinical and experimental research is discussed. We argue that a change in the ratio of n-6/n-3, especially during early life, may induce developmental changes in brain connectivity, synaptogenesis, cognition and behavior that are directly related to ASD.

Contents

Abbreviations: AA, arachidonic acid; ADHD, attention deficit hyperactivity disorder; α-LA, alpha-linolenic acid; ASD, autism spectrum disorders; DHA, docosahexaenoic acid; EFA, essential fatty acids; EPA, eicopentaenoic acid; FABP, fatty-acid-binding protein; Fads2, fatty acid desaturase 2; FAO, fatty acid oxidation; GABA, gamma-amino butyric acid; IL-1, interleukin-1; LA, linoleic acid; n-3, omega-3; n-6, omega-6; PGE_2, prostaglandin E_2; PLA_2, phospholipase A_2; PLC, phospholipase C; PPAR, peroxisome proliferator-activated receptors; PUFA, polyunsaturated fatty acids; TNF, tumor necrosis factor.

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1. Introduction

The role of polyunsaturated fatty acids (PUFAs) in brain development and neurodevelopmental disorders is a relative new and challenging area of neurobiological research. PUFAs play an important role in the structure and function of the neuronal cell membranes in brain, as well as in the development and homeostasis of the retina and myelin sheath (Alessandri et al., 2004; Guesnet and Alessandri, 2011; Meguid et al., 2008; van de Rest et al., 2012; Wallis et al., 2002). Recently, clinical trials have been conducted to supplement omega-3 (n-3) PUFAs to patients with various neuropsychiatric developmental disorders such as attention deficit hyperactivity disorder (ADHD), bipolar disorder and schizophrenia (Amminger et al., 2007; Politi et al., 2013; Richardson, 2004a,b, 2006; Sinn et al., 2008). In contrast to ADHD, less is known about a possible role of PUFAs in the emergence of the other major class of neurodevelopmental disorders; autism spectrum disorders (ASD) (Sliwinski et al., 2006).

About 1 in 68 children display signs and symptoms that lead to a diagnosis of autism spectrum disorder (ASD) (Baird et al., 2006; Centers for Disease Control and Prevention, 2014; Weintraub, 2011). Clinically, ASD is defined by impairments in social interaction and communication, and by restricted, repetitive and stereotyped behavior and interests. The prevalence of ASD diagnosis has shown an exponential rise in the last two decades (Fig. 1) (American Psychiatric Association, 1987, 2000; Fombonne, 2009; Fombonne et al., 2009; Nazeer and Ghaziuddin, 2012; Rutter, 1978; Weintraub, 2011). About 50% of this rise seems accounted for by factors such as broader diagnostic criteria, lower thresholds for clinical diagnosis or higher parental age, leaving roughly 50% of the increase unexplained (Weintraub, 2011). Epidemiological studies have indicated that environmental events such as prenatal infections, teratogenic and air pollutant exposure may also be considered as risk factors for ASD (Chaste and Leboyer, 2012; European Commission, 2005; Duchan and Patel, 2012; Larsson et al., 2005; Volk et al., 2011; Wing and Potter, 2002). Changes in dietary composition have also been put forward as candidate environmental factors contributing to autistic development. In addition, environmental factors, such as maternal folic acid levels, oxidative stress and ischemia are also important during brain development (Das, 2013). The intensity by which these factors influence brain development may depend on individual variation in epigenetic (e.g., Burdge and Lillycrop, 2014) and genetic regulation following environmental exposure. One of the suggested changes in dietary content may relate to alterations in PUFA intake. This notion was derived from studies that associated PUFA concentrations to ASD diagnoses (Amminger et al., 2007; Bell et al., 2004; El-Ansary et al., 2011a,b; Meguid et al., 2008; Meiri et al., 2009; Vancassel et al., 2001; Yui et al., 2012) and preliminary evidence shows that n-3 PUFA supplementation may reduce ASD symptomatology (Meguid et al., 2008). However, more studies are needed to strengthen this finding. Interestingly, mutations in genes encoding Fatty acid binding proteins (FABP) 7, 5, and 3 have been associated with autism and schizophrenia in Japanese subjects (Maekawa et al., 2010). The understanding of the mechanisms of PUFAs in ASD pathogenesis will be complex as PUFAs have broad and diverse biological actions. Here, we review basic PUFA physiology and neurobiological actions and relate these to a possible involvement of PUFAs in ASD. We focus our review on changes in the PUFA n-6/n-3 ratio as major dietary changes in the last decade have caused a major shift in this ratio.

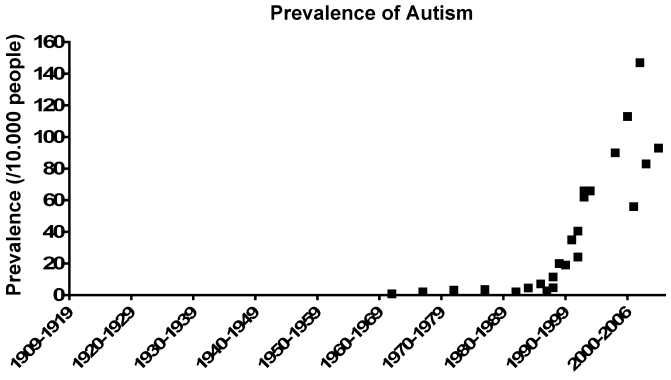

Fig. 1. The ASD prevalence (measured in the USA) has been rising exponentially over the last fifty years (Centers for Disease Control and Prevention, 2007, 2009, 2012, 2014; Gurney et al., 2003; Manning et al., 2011; Newschaffer et al., 2005; Nicholas et al., 2008; Ritvo et al., 1989; Yeargin-Allsopp et al., 2003). ASD prevalence is indicated based on the year of birth. The marked rise in births of children with ASDs began in the late 1980s, in the period that the oil consumption plateaued at around 45% of total dietary energy intake.

2. PUFAs: nomenclature

Polyunsaturated fatty acids (PUFAs) are fatty acids that contain carbon chains with more than one double bond. PUFAs can be categorized in various groups on the basis of their chemical structure and the position of the first double bond counted from the methyl terminus; omega-3 (n-3), n-6, n-7 and n-9, divides them in different groups. The most important components are the essential fatty acids (EFAs), n-6 linoleic acid (LA) and n-3 alpha-linolenic acid (α-LA), that cannot be metabolized by the body and are required from dietary intake (Fig. 2) (Berg et al., 2007; Schmitz and Ecker, 2008; Wallis et al., 2002). N-6 and n-3 EFAs are the precursors of the n-6 arachidonic acid (AA) and n-3 docosahexaenoic acid (DHA) and n-3 eicosapentaenoic acid (EPA). EFAs are converted into these active long-chain PUFAs by a communal set of enzymes (Fig. 2). Thus, concentrations of n-6 AA and n-3 DHA and EPA depend on the EFA concentrations, as they compete for the same conversion enzymes (see Fig. 2) (Eckert et al., 2012; Guesnet and Alessandri, 2011; Kris-Etherton and Hill, 2008; Pawlosky et al., 2001; Salem et al., 1999; Wallis et al., 2002). This enzyme competition is an important factor to appreciate the consequences of changes in the availability of n-6 of n-3 PUFAs. Several processes, such as bioavailability and oxidation influence n-3 and n-6 activity. For example, fatty acids need to bind to proteins to be effective in the body, such as fatty acid binding proteins (FABPs). These FABPs are able to bind long chain fatty acids. The level of FABP availability is, therefore, an important determinant of n-3 and n-6 bioavailability. In addition, unsaturated fatty acids in air exposed food are vulnerable to oxidation (Chaiyasit et al., 2007). Oxidative deterioration influences many quality characteristics of food, such as flavor (rancidity), color, texture, but

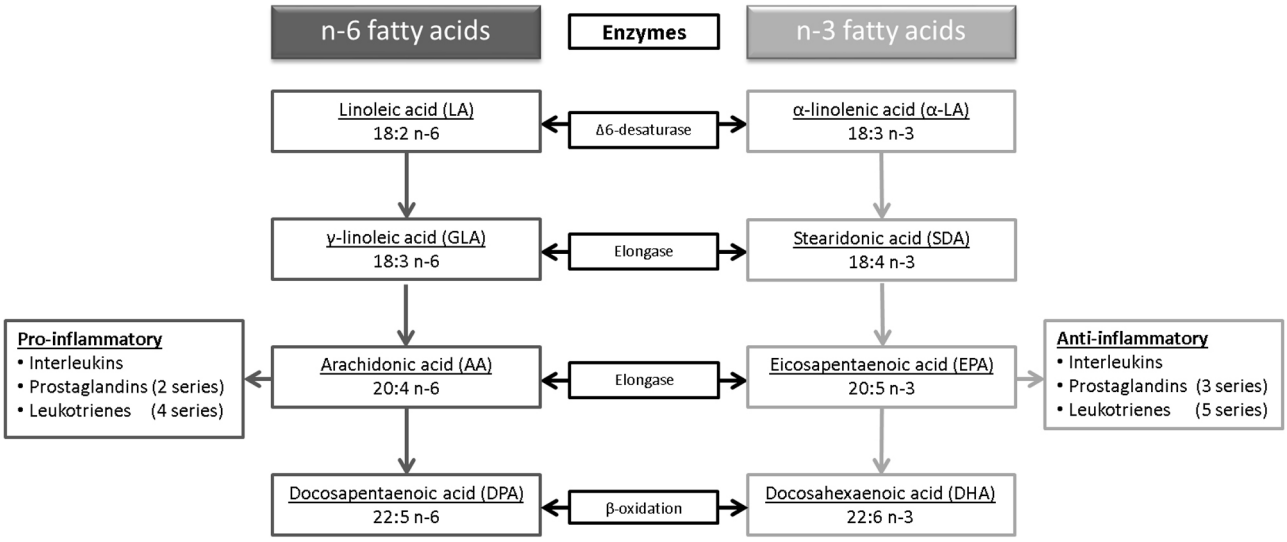

Fig. 2. A simplified overview of the polyunsaturated fatty acid pathway. Omega-6 and omega-3 fatty acids are taken up as essential fatty acids (EFAs; LA and α-LA) through food consumption. Due to enzyme competition, the fatty acids will be converted into the long-chain PUFAs AA and DHA, depending on the amount of EFAs that are available. Due to the competition there will be an adverse effect: an increase in omega-6 will lead to a decrease in omega-3 and vice versa.

also produces potentially toxic compounds (Halliwell et al., 1995; Kubow, 1992, 1993; Liu and Huang, 1995).

3. PUFAs and basic physiology

Generally PUFAs have three main functions in the body. First, fatty acids are a main component of phospholipids, which are the major constituent of cellular membranes (Brooker et al., 2008; Innis, 1991; Glomset, 2006). N-6 and n-3 PUFAs are fundamental components of these phospholipids (Martinez and Mougan, 1998), as their concentration in phospholipids can influence the biophysical properties of the lipid bilayer. In particular, n-6 AA and n-3 DHA PUFAs are enriched in the membranes of neural tissue where they mediate signal transduction (Martinez and Mougan, 1998). This role in signal transduction related to the fluidity of cell membranes is partially determined is by the fatty acid content of the membrane phospholipids. The membrane fluidity is important for receptor functioning and recycling as well as for the efficiency of signaling pathways. The presence of n-3 PUFAs in the cell membrane enhances the fluidity, which thus may be an essential aspect of the neurological effects of n-3 PUFA (Christensen et al., 2011; Green et al., 2008). The fatty acid content of tissue membranes changes throughout development, for example through progressive incorporation of n-3 DHA (Breckenridge et al., 1972; Brooker et al., 2008; Innis, 1991; Martinez and Mougan, 1998). Therefore, it seems that n-6 and n-3 PUFAs have different effects by influencing membrane fluidity and the PUFA ratio, n-6/n-3, is important in this respect (Christensen et al., 2011; Green et al., 2008; Wallis et al., 2002; Whelan, 2008; Yehuda et al., 2001).

In addition to cell membranes, both non-myelin as myelin neurite membranes also contain high concentrations of n-6 AA and n-3 DHA, respectively, 50% and 70% of the total amount of membrane lipids (Bourre, 2004; Innis and de La Presa Owens, 2001; Yehuda et al., 2005b). Together, it is evident that high amounts of n-6 AA and n-3 DHA are required for synaptogenesis and the maturation of nerve growth cones (Martin and Bazan, 1992).

The second major function of PUFAs is that n-6 and n-3 PUFAs have been identified as endogenous ligands for peroxisome proliferator-activated receptors (PPARs) (Abbott, 2009). PPARs are nuclear receptor proteins, functioning as transcription factors that regulate gene expression in metabolic processes relating to cellular differentiation and development (Michalik et al., 2006). PPARs are divided in three primary subtypes, Alpha (PPARα), Beta (PPARβ) and Gamma (PPARγ) (Abbott, 2009; Aoyama et al., 1998; Innis, 1991; Michalik et al., 2006). The PPAR subtypes are widely expressed throughout the brain, especially in areas concerning learning and memory, such as the hippocampus (Hajjar et al., 2012).

N-6 and n-3 PUFAs have been identified as endogenous ligands for PPAR, inducing gene expression in signaling pathways that regulate cellular processes, such as myelination and lipid homeostasis (Abbott, 2009). Supplementation with n-3 PUFAs in P7 C57BL6J mice leads to an increase in PPARγ expression in brain, which was not observed in later developmental stages. In contrast, n-3 PUFA deficiency did not cause an alteration in PPARγ levels (Tian et al., 2011). At more adult ages, it was shown that in rat forebrain, PPARγ expression is significantly reduced. It has been suggested that this decline may contribute to age related cognitive decline and has led to the hypothesis that n-3 EPA and DHA supplementation may be used to slow down this process (Dyall et al., 2010). Rodent studies have shown that the expression of PPARs is inversely related to the n-6/n-3 ratios in diet, i.e., increased PPARα and PPARγ expression at lower n-6/n-3 PUFA ratio (Hajjar et al., 2012; Tian et al., 2011). An identical observation was made in rats from 3 weeks of age where different n-6/n-3 ratios can improve PPAR gene expression, accompanied by changes in spatial memory performance (Hajjar et al., 2012). Importantly, variations in PPAR related genes that contribute to fatty acid metabolism have been associated with ASD and metabolic syndrome X (Clark-Taylor and Clark-Taylor, 2004; Das, 2006; Maekawa et al., 2010; Yoo et al., 2008). Components required for fatty acid metabolism, such as carnitine, are reduced in autistic children (Filipek et al., 2004). Carnitine deficiency has been correlated with decreased levels of n-3 DHA, which could indicate a shared pathway underlying ASD. Furthermore, carnitine deficiency can indicate of fatty acid oxidation (FAO) disorder (Clark-Taylor and Clark-Taylor, 2004). Interestingly, a case study of a patient with autism and a disorder in FAO described lower plasma fatty acid levels of n-3 DHA and EPA but normal levels of n-6 PUFAs and n-3 EFAs (Clark-Taylor and Clark-Taylor, 2004).

The third domain of PUFA action is that they are precursor of a range of molecules engaged in inflammatory processes, such as the eicosanoids prostaglandins and interleukins. These eicosanoids origin from oxidation of 20-carbon fatty acids (Fig. 2) (Bourre, 2004; Innis, 1991). In this capacity, n-6 and n-3 PUFAs have divergent

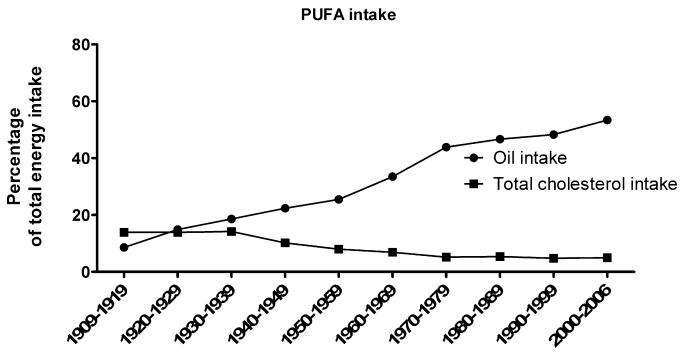

Fig. 3. The dietary change in fatty acid intake in the USA related to the rise in autism prevalence. The oil intake in the USA (vegetable oils, salad dressings, cooking oils) has been rising since beginning of the 20th century. The cholesterol intake changed when, in the early 1960s, cholesterol was replaced by vegetable oils, due to the effect of cholesterol on cardiac diseases (Gerrior et al., 2004; Hiza and Bente, 2011).

functions; n-6 PUFAs are pro-inflammatory precursors, whereas n-3 PUFAs are anti-inflammatory precursors (Green et al., 2008; Wallis et al., 2002; Yehuda et al., 2005b). As a consequence, n-6/n-3 ratio influences immune status, e.g., a relative increase of n-3 results in a decrease of inflammatory metabolites and an increase synthesis of less inflammatory or anti-inflammatory signaling molecules (eicosanoids) (Calder and Grimble, 2002). For instance, n-3 PUFAs suppress synthesis of IL-1, 6 and 12, prostaglandin E_2 (PGE_2) and TNF and improve synthesis of IL-2. N-6 fatty acids have the opposite effect on the synthesis of these molecules (Simopoulos, 2002; Yehuda et al., 1999, 2001, 2005a). In addition, n-6 and n-3 PUFAs give rise to new classes of signaling lipids with acute inflammatory properties, for example prostaglandins and leukotriene B_4 (Fig. 2) (Serhan et al., 2008). N-3 fatty acids also inhibit the production of n-6 AA derived pro-inflammatory cytokines, such as interleukins, independent of the production of n-6 or n-3 derived eicosanoids (Calder and Grimble, 2002; Laye and Dantzer, 2006).

4. Changes in PUFA dietary intake

The food supply and diet has changed significantly, since we evolved from hunter–gatherers in the Paleolithic era 10,000 years ago. The Paleolithic green leafy vegetables and fruits diet contained limited fat intake with a balanced n-6/n-3 polyunsaturated fatty acids ratio of 1:1 (Burr and Burr, 1930; Innis, 2008; Keys et al., 1957; Kritchevsky, 1998; Sanders, 1999; Simopoulos, 1999, 2011). 80 years ago, artificial vegetable derived oils, such as canola and soybean oils, were produced for the first time (Fig. 3). Initially, the consumption of these oils in products such as margarine, oils and salad dressings was limited and mainly used as a replacement of cholesterol for reasons of vascular risk. In 1986, the intake of n-6 rich oils took a dramatic rise in our diets as they became commercially available on the market (Fig. 3) (Blasbalg et al., 2011; Burr and Burr, 1930; Crawford, 1968; Innis, 2008; Keys et al., 1957; Kritchevsky, 1998; Simopoulos, 1999, 2011). The market introductions of these artificial vegetable oils has led to an 167- and 1163-fold increase of canola and soybean oils use, respectively. This increase is due to the fact that these oils were barely consumed before the introduction in 1986 (Blasbalg et al., 2011) (Fig. 3). These dietary changes were not limited to humans; the new oils were also used as add-ons in livestock diet. As a consequence, the consumption of meat products from livestock became an additional source of n-6 fatty acids (Crawford, 1968). Overall, modern diets contain increased n-6/n-3 ratio's (10–25:1), which may influence the effects of PUFAs on the whole human metabolism (Cordain et al., 2005; Eaton and Eaton Iii, 2000; Eaton et al., 1998; Simopoulos, 1999, 2011).

The impact of these PUFA ratio changes on neurodevelopment will depend on the developmental stage and duration of changes of the exposure to PUFA ratios changes. The last trimester of pregnancy is a crucial phase, as large amounts of n-6 AA and n-3 DHA are needed for the synthesis of membrane phospholipids to complete fetal brain development and neurogenesis (Coti Bertrand et al., 2006; Innis and de La Presa Owens, 2001; Kawakita et al., 2006). The transport of n-3 fatty acids to the unborn child in this period is highly dependent on maternal dietary intake (Bernardi et al., 2012; Green et al., 2008; Greenberg et al., 2008; Guesnet and Alessandri, 2011; Luchtman and Song, 2013; Schiefermeier and Yavin, 2002). Furthermore, the passage of n-6 and n-3 PUFAs across the fetal blood brain barrier depends on the relative amounts of fatty acids in the blood of the fetus, further indicating the need of a balanced maternal diet (Chen et al., 2008; Green et al., 2008).

The importance of PUFA uptake mechanisms also has consequences for postnatal dietary intake. The intake of n-3 DHA in children is higher in breast-fed versus formula-fed children as the n-3 DHA content is much lower in formula milk diets. Only formulas with preformed n-3 DHA have the ability to match the concentration to that of breast-fed children (Alessandri et al., 2004; Wainwright, 1992).

5. PUFAs and brain development

Various studies in animals have investigated the consequences of PUFA deficiencies on neurodevelopment. Both *in vitro* and *ex vivo* studies with cultured mice neurons have indicated that PUFAs play an important role in dendritic growth and synaptogenesis of neuronal cells. For example, cultured embryonic hippocampal neurons that were treated with n-3 DHA supplementation showed an increase in neuronal cell survival, neurite growth, synaptogenesis and glutamatergic synaptic activity (Cao et al., 2009; Kim et al., 2011). These findings are consistent with studies in which the offspring of rats maintained on an n-3 deficient diet showed impaired hippocampal neurite growth and synaptogenesis (Calderon and Kim, 2004; Kim et al., 2011). Furthermore, it has been shown that fetal mouse hippocampal cell-cultured neurons, obtained from pups also raised under n-3 DHA depletion conditions, have an aberrant development. The n-3 depleted neurons showed shorter neurites, less branches and dendritic arborization, decreased expression of synapsins and less synapsin-positive puncta (Cao et al., 2009; Kim et al., 2011). Interestingly, supplementation with n-3 DHA seems to (partially) restore some of these effects on spine and dendrite maldevelopment (Calderon and Kim, 2004; Cao et al., 2009; Kim et al., 2011). In contrast, one of these studies also tried n-6 AA supplementation in rats, which was unsuccessful in restoring neuronal defects (Calderon and Kim, 2004).

These findings are highly important as they indicate that n-3 fatty acid deficiency affects neuronal plasticity, which seems at least partially reversible via n-3 fatty acid supplementation (Cao et al., 2009; Kim et al., 2011). In the same context, PUFAs have also been shown to exert a function in synapse formation via their effects on the maturation of growth cones to mature synapses in mice. This was indicated with the finding that endogenous n-3 DHA levels increase in the membrane of growth cones before they develop into mature synapses. Interestingly, the subsequent maturation to synapses is characterized by an increase in n-6 AA while the initial rise in n-3 DHA declines (Martin and Bazan, 1992).

As mentioned above, an important aspect of PUFAs is their importance in the active phase of myelin synthesis (Bourre, 2004).

Both animal and human studies revealed that deficiency of n-3 EPA during the most important phase of myelination (first 6 weeks postnatally) will lead to amyelination, dysmyelination or demyelination. As a consequence, it may be expected that early life dietary changes in PUFAs intake may influence myelination of newly formed circuitries (Poduslo and Jang, 1984; Salvati et al., 2000; Yehuda et al., 2005b).

How can these broad effects of PUFAs be implicated in the development of autism spectrum disorders? Interestingly, several described neurodevelopmental effects of PUFA ratio change overlap with putative pathogenic mechanisms in ASD. For instance, the significant effects on neuronal morphology, e.g., synapse formation and neurite outgrowth resulting from n-3 deficiency or n-3 supplementation have been indicated as core mechanisms in ASD pathology (Delorme et al., 2013) and in particular the possible effects of PUFA change on synapse dynamics in early life (Courchesne, 2002; Courchesne and Pierce, 2005; Ebert and Greenberg, 2013; Pardo and Eberhart, 2007). Furthermore, the sex difference in metabolic conversion of PUFAs seems to be in accordance with the male pre-dominance observed in ASD (Bell et al., 2000; Burdge and Wootton, 2002; James et al., 2011; Richardson and Ross, 2000). The conversion of n-3 α-LA to n-3 DHA is severely restricted in males (0% conversion) compared to females (9% conversion), which could explain the sex ratio of ASD incidence, as males are 3–4 times more affected compared to females (Burdge and Wootton, 2002; Richardson and Ross, 2000). This aspect particularly is more relevant during development, as isotopic tracer studies show that the conversion of n-3 α-LA to n-3 DHA is of the order of 1% in infants, and considerably lower in adults (Brenna and Lapillonne, 2009).

Another link of PUFA to ASD may come from the emerging theory of aberrant long-range brain connectivity in ASD (Courchesne, 2002; Courchesne and Pierce, 2005). This theory posits that ASD is involved in the disruption of white matter tracts in social cognition related brain regions. Indeed, alterations of connectivity across different brain regions have been indicated in ASD (Herbert, 2005; Herbert et al., 2003; Won et al., 2013). As pointed out, white matter tract formation and myelin synthesis is very sensitive to the ratio of n-6/n-3 PUFAs. A deficiency of n-3 or an increase in n-6 could lead to changes in myelination and thereby alter connectivity (Poduslo and Jang, 1984; Salvati et al., 2000; Yehuda et al., 2005b). Future experiments in mice, through dietary intervention with omega-3 and omega-6 fatty acids, will be necessary to reveal the impact of PUFAs on myelin synthesis and white matter tract formation.

6. PUFAs and behavior in mice and men

A large set of behavioral phenotype changes have been observed in relation to n-3 deficiency or supplementation. First, pre and postnatal n-3 deficiency has repeatedly been shown to lead to higher levels of anxiety in rats and mice. Subsequent postweaning n-3 supplementation reduced the anxiety levels in 4-month-old mice to the levels of control animals, where n-6 supplementation increased these levels (Carrie et al., 2000; Jones et al., 2013; Larrieu et al., 2012; Takeuchi et al., 2003). Certain aspects of learning and memory are also affected in n-3 deficient animals. For example, third generation n-3 deficient Long–Evans rats, all generations are continuously fed on this deficient diet, showed impairments in the learning trial of the Morris water maze (Moriguchi et al., 2000). Furthermore, fatty acids can modulate locomotor activity levels. Prenatal and both pre- and postnatal exposure to high n-6 fatty acids led to higher locomotor activity in several mouse strains compared to their controls, where n-3 supplementation could rescue this phenotype (Raygada et al., 1998; Umezawa et al., 1995; Vinot et al., 2011). In addition, a pre- and postnatal diet rich in n-6 PUFAs until weaning has a negative effect on social behavior in mice (Jones et al., 2013). It is notable that other studies found opposite or no effects of different n-3 deficiency supplementation on behavior using different rodent strains (Frances et al., 1995; Levant et al., 2004; Nakashima et al., 1993; Raygada et al., 1998; Umezawa et al., 1995; Vinot et al., 2011). This might indicate an important effect of genetic background on the effect size of n-3 depletion on behavioral outcome.

The above-mentioned animal studies clearly show that n-3 depletion and subsequent supplementation can influence behavioral and cognitive performance. For example, prenatal or prenatal and postnatal n-3 deficiency results in deficits in learning and memory performances, which can partly be reversed by n-3 supplementation in adulthood (Anderson et al., 2005; Chung et al., 2008; Guesnet and Alessandri, 2011). These effects on motor behavior and cognitive performance may be in particular relevant to ASD symptomatology. At this stage, it is unknown how PUFA ratio changes affect behavior during early stages of life as the behavioral data, thus far, has been collected in adult rodents. This has an important relevance as research has indicated that the 3rd trimester of pregnancy and the first 6 months of human life are the most important period for the uptake of n-3 DHA in the brain. In the last trimester of pregnancy the fetal brain undergoes increased neurogenesis and cell maturation. Rapid DHA accumulation takes place, unparalleled to the increase of other fatty acids. During the first six months of post-natal life the brain experiences the highest accumulation of DHA, which is important for the rapid brain development. Accretion then represents 50% of the total-body accretion, indicating a very selective DHA uptake mechanism by the blood brain barrier in this important period (Bernardi et al., 2012; Guesnet and Alessandri, 2011; Luchtman and Song, 2013; Schiefermeier and Yavin, 2002).

Together, it will be important to translate the effects of PUFA ratio changes on brain development and behavioral and cognitive performance in rodents to human subjects. Human studies indicate a critical window for PUFA intervention based on the dynamics of DHA accumulation during early life. However, rodent studies indicate that, in addition to this early life developmental stage, PUFA ratio changes may also be partially effective in altering behavioral and cognitive performance when applied in adulthood. Further research is necessary to understand how PUFA's may alter behavior and cognitive processes in view of developmental stage. It should be taken in account that extrapolation of results between mice and men is difficult, for example, it is known that they have different metabolic rates (Kopecky et al., 2009). The initial and preliminary study of n-3 PUFA supplementation in autistic children suggest a beneficial effect on concentration, eye contact, language development and motor skills in children with ASD (Meguid et al., 2008). In addition, n-3 supplementation may ameliorate other ASD symptoms (James et al., 2011; Meguid et al., 2008). However, other clinical studies on PUFAs revealed little to even opposite effects on ASD behavior (Amminger et al., 2007; Bent et al., 2011; James et al., 2011; Yui et al., 2012). Behavioral studies in rodents and humans are necessary to unravel and better understand the relationship between PUFAs, brain development and behavior.

7. PUFAs and ASD

7.1. PUFAs, inflammation and ASD

The relationship between PUFAs and inflammatory homeostasis in ASD has been triggered as up to 60% of autism patients have some systemic immune dysfunction (Pardo and Eberhart, 2007). It is therefore understandable that a number of attempts have been made to attenuate inflammation with treatments like n-3 PUFAs

and PPARγ agonists (Hendren et al., 2009; Pardo and Eberhart, 2007). However, if at all, it is not known if immune activation is an initiating or chronic factor in the pathogenesis of ASD (Careaga et al., 2010). Nonetheless, a consistent observation has been the observation of ongoing neuro-inflammation in brain specimens of ASD individuals (Careaga et al., 2010; Onore et al., 2012; Vargas et al., 2005; Won et al., 2013).

This increased immunoreactivity may be related to increased dietary n-6/n-3 PUFA ratios. This may lead to an overproduction of n-6 derived pro-inflammatory cytokines (Greenberg et al., 2008; Simopoulos, 2002). These molecules have important effects on brain physiology, such as blood flow and biological membrane permeability, and have been shown to affect cognitive brain functions, important for ASD (Bourre, 2004; Schmitz and Ecker, 2008; Serhan et al., 2008; Yehuda et al., 1999, 2005a). N-6 AA is also an important source of prostaglandins and thus high concentrations of n-6 AA results in more biologically available pro-inflammatory n-6 AA derived eicosanoids (Fig. 2) (Berg et al., 2007; Fokkema et al., 2000; Wainwright, 2002; Yehuda et al., 2001, 2005a). These n-6 AA derived prostaglandins (Fig. 2), among others, contribute to allergies and inflammatory disorders, conditions which are frequently comorbid to ASD (Depino, 2013; Gesundheit et al., 2013; Onore et al., 2012; Simopoulos, 2006; Yehuda et al., 2001). Furthermore, n-6 derived prostaglandins are associated to the initiation of (preterm) labor, whereas n-3 derived prostaglandins promote relaxation of myometrium and therefore elongate pregnancy duration (Greenberg et al., 2008; Olsen et al., 1992). This function in labor physiology may indirectly be related to ASD as prematurity is an important risk factor for autistic brain development (Mahoney et al., 2013). Another putative immunological mechanism in ASD has been indicated by elevated levels of autoantibodies to neuronal and glial molecules in autistic patients that may be ascribed to a n-6/n-3 PUFA ratio disturbance (Won et al., 2013). Overall, the role of inflammatory processes in ASD could be modulated by changes in PUFA ratios and could provide an important entry to study the effects of PUFA supplementation treatment (Hagberg et al., 2012).

7.2. PUFAs and neurotransmitter changes related to ASD

The complex role of PUFA in membrane and signal transduction has been related to changes in neurotransmitter physiology, such as dopamine and serotonin synthesis. In animals studies, a prenatal and postnatal (days 0–18) EFA deficient diet, respectively, in rats and piglets, resulted in decreased serotonin neurotransmitter concentrations in the frontal cortex, suggesting a role of n-3 DHA and n-6 AA in neurotransmitter synthesis or turnover (de La Presa Owens and Innis, 1999; Innis and de La Presa Owens, 2001). N-3 DHA depletion in pre-adolescent rats also resulted in a decrease in prefrontal cortex serotonin, where post-pubescent DHA deficiency did not alter the prefrontal cortex serotonin levels.

Furthermore, in normal development, serotonin synthesis capacity in children, aged 2–5 years, is higher than that of adults, where the decline to adult levels occurs between the age of 5 and 14 years. These findings may be important for ASD as age-dependent changes of serotonin synthesis are absent in autistic children, resulting in lower levels of serotonin, compared to age-related non-autistic children (Chugani et al., 1999; Herault et al., 1996; Pardo and Eberhart, 2007; Schain and Freedman, 1961). Indeed, increased serotonin levels in whole blood, related to clinical severity, are a consistent finding in ASD (Burgess et al., 2006; Herault et al., 1996). These findings could indicate that n-3 DHA and the maturation and resilience of the central serotonin synaptic transmission system are linked to perinatal periods (McNamara et al., 2009). It is intriguing in this respect that the manipulations of PUFAs or serotonin in developing animals seem to recapitulate some of the pathological findings in the brains of patients with ASD, such as an increase in hippocampal cell number and reduction of neuronal cell size (Bauman and Kemper, 1985, 2005; Blatt and Fatemi, 2011; Chugani et al., 1999; Cook et al., 1997; McDougle et al., 1996).

A role for the main inhibitory neurotransmitter γ-amino butyric acid (GABA) has been established in ASD pathogenesis; GABA dysfunction has been suggested by clinical, neuropathological and genetic studies (Hamazaki and Hamazaki, 2008). For instance, reduction in the GABAergic receptor system has been found in brain tissue of autistic patients, which yielded information about 3 genes for specific subunits of the $GABA_A$ receptor (Hamazaki and Hamazaki, 2008). Interestingly, bicuculline, a $GABA_A$ receptor antagonist, dramatic increased the effects of n-3 DHA deficiency in rats. However, bicuculline did not affect the influence of n-3 DHA supplementation. These results are consistent with the observed inhibition of muscimol action, another $GABA_A$ receptor agonist, by n-3 DHA. Together, these findings suggest that n-3 DHA prevents blocking or modulation of the activity of the $GABA_A$ receptor (D'Hulst et al., 2009; Schwartz and Yu, 1992; Takeuchi et al., 2003). This n-3 DHA effect might be the result of an altered lipid environment surrounding GABA receptor complexes or through action on novel receptor sites. At least they suggest that n-3 DHA deficiency alters GABAergic activity (Takeuchi et al., 2003), which may be an important link between PUFAs and ASD pathogenesis (Hamazaki and Hamazaki, 2008; Pardo and Eberhart, 2007; Schroer et al., 1998).

A second way of PUFAs interacting with GABA neurotransmission interacting is through the actions of PLA_2 (Phospholipase A_2), a compound derived from membrane phospholipids. PLA_2 has been shown to decrease the chloride flux induced by barbiturates in the cerebral cortex and is therefore thought to inhibit $GABA_A$ receptor function (Roseth et al., 1998). This is interesting as increased levels of n-6 AA increase neuronal excitability through PLA_2 or phospholipase C (PLC) activation by inhibiting $GABA_A$ neurotransmission (Schwartz and Yu, 1992). Interestingly, activation of PLA_2, PLC and release of n-6 AA and n-6 metabolites is triggered by ischemia and seizure activity. These studies showed that fatty acids have a complex effect on the binding characteristics of the GABA/benzodiazepine receptor, but further research is required (Koenig and Martin, 1992; Schwartz and Yu, 1992).

It should be noted that the recuperation process of n-3 fatty acids after adequate supplementation in rats and monkeys takes weeks to recover fully and may not lead to a complete reversal of symptoms. This delay in recuperation effect on behavioral and cognitive systems may be dependent on the way that different neurotransmitter synthesis processes are influenced as a function of supplementation. For instance, prenatal n-3 PUFA deficiency results in alterations of the mesocortical and mesolimbic dopamine neurotransmitter systems in rat brain (Anderson et al., 2005; Chung et al., 2008; Guesnet and Alessandri, 2011). However, n-3 supplementation will not completely reverse the dopaminergic alterations that are associated with fronto-limbic dysfunction in frontal cortex (Anderson et al., 2005; Chung et al., 2008; Moriguchi et al., 2001; Wainwright, 2002; Yehuda et al., 2005b). These partial effects seem to reflect brain-region specificity of n-3 supplementation efficacy. Indeed, studies have shown that the restoration of n-3 DHA levels, due to supplementation of n-3 DHA, is different in the frontal cortex compared to the striatum and cerebellum (Delion et al., 1996). This brain region specificity of PUFA turn-over may also be reflected in behavioral expression of PUFA deficiency. Frontal region related functions such as executive dysfunctioning or motor problems may be more vulnerable to PUFA ratio changes and only show partial response to n-3 supplementation (Delion et al., 1994, 1996; Levant et al., 2004; Zimmer et al., 2000).

8. Discussion

This review shows that n-6/n-3 PUFA ratio disturbances during early life can affect major processes in brain development and induce aberrant behavior. Most effects of PUFA changes may take place early in life through maternal depletion and/or early postnatal diets change (e.g., formula feeding) and seem to influence brain maturation and synaptic development. Dietary n-6/n-3 PUFA ratio changes, and specifically those related to n-3 deficiency, may induce early life effects on myelination, neurogenesis, synaptogenesis, neurotransmitter synthesis and turn over, PPAR expression and inflammatory responses.

In addition to these changes in brain development processes, experimental PUFA ratio changes have clearly shown to induce changes in behavioral expression. These behavioral changes are mainly observed in the domains of anxiety, locomotor activity and learning and memory.

Here, we put forward that the recent rigorous change in dietary n-6/n-3 ratio, i.e., the introduction of vegetable oils and the removal of cholesterol, may be an important environmental factor in the increase of ASD related problems. In support of this hypothesis, a small set of human studies have shown that autistic children have deficits in fatty acids levels (Bell et al., 2004; El-Ansary et al., 2011a,b; Meguid et al., 2008; Vancassel et al., 2001), but additional studies are required to confirm these findings. Furthermore, preliminary results show that n-3 PUFA supplementation in autistic children can significantly improve concentration, eye contact, language development and motor skills (Al-Farsi et al., 2013; Bell et al., 2004; El-Ansary et al., 2011a,b; Meguid et al., 2008; Vancassel et al., 2001).

From a neurodevelopmental perspective, both human and animal studies indicate that the 3rd trimester of pregnancy and the first 6 months of life are the most important period for the uptake of n-3 DHA in the brain. Targeting this critical window of development with n-3 supplementation, thereby influencing the n-6/n-3 ratio, may reveal more information about the role of PUFA ratio changes on developmental trajectories of maladaptive behavior and cognitive deficits. This could also provide enhanced understanding of neuropathological mechanisms in ASD and lead to the development of novel add-on treatment opportunities in ASD. Such studies should also learn if the parallel time line of dietary changes (Fig. 3) and sudden rise in ASD diagnosis (Fig. 1) have a functional relationship.

Together, based on the materials reviewed here, it seems important to consider the effect of absolute or relative n-3 deficiencies in the etiology and treatment of ASD.

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