NEURO-SIGNALS

Neurosignals 2010;18:98–112
DOI: 10.1159/000323189

Received: August 18, 2010
Accepted after revision: November 29, 2010
Published online: February 4, 2011

The Neurobiology of Lipid Metabolism in Autism Spectrum Disorders

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Key Words
Autism · Abnormal fatty acid metabolism · Dietary supplementation · Genetic defects · Arachidonic acid · Prostaglandins

Abstract
Autism is a neurodevelopmental disorder characterized by impairments in communication and reciprocal social interaction, coupled with repetitive behavior, which typically manifests by 3 years of age. Multiple genes and early exposure to environmental factors are the etiological determinants of the disorder that contribute to variable expression of autism-related traits. Increasing evidence indicates that altered fatty acid metabolic pathways may affect proper function of the nervous system and contribute to autism spectrum disorders. This review provides an overview of the reported abnormalities associated with the synthesis of membrane fatty acids in individuals with autism as a result of insufficient dietary supplementation or genetic defects. Moreover, we discuss deficits associated with the release of arachidonic acid from the membrane phospholipids and its subsequent metabolism to bioactive prostaglandins via phospholipase A_2-cyclooxygenase biosynthetic pathway in autism spectrum disorders. The existing evidence for the involvement of lipid neurobiology in the pathology of neurodevelopmental disorders such as autism is compelling and opens up an interesting possibility for further investigation of this metabolic pathway.

Introduction

Autistic disorder is a behaviorally defined neurodevelopmental disorder of childhood characterized by deficits in social interaction, language, communication and repetitive behaviors that manifest in early postnatal life [1]. It belongs to a spectrum of closely related conditions also referred to as autism spectrum disorders (ASDs) that also includes pervasive developmental disorder not otherwise specified, Asperger's syndrome, and childhood disintegrative disorder. The incidence of ASDs has increased significantly over the last decades and is currently 1 in 150, affecting boys four times more often than girls [2, 3]. A strong genetic component is indicated by the high concordance rates in monozygotic twins (70–95%) versus dizygotic twins (0–23%) [1, 4–6]. Many genes have been implicated in the etiology of the disorder [4] in addition to the contributing environmental factors [7–

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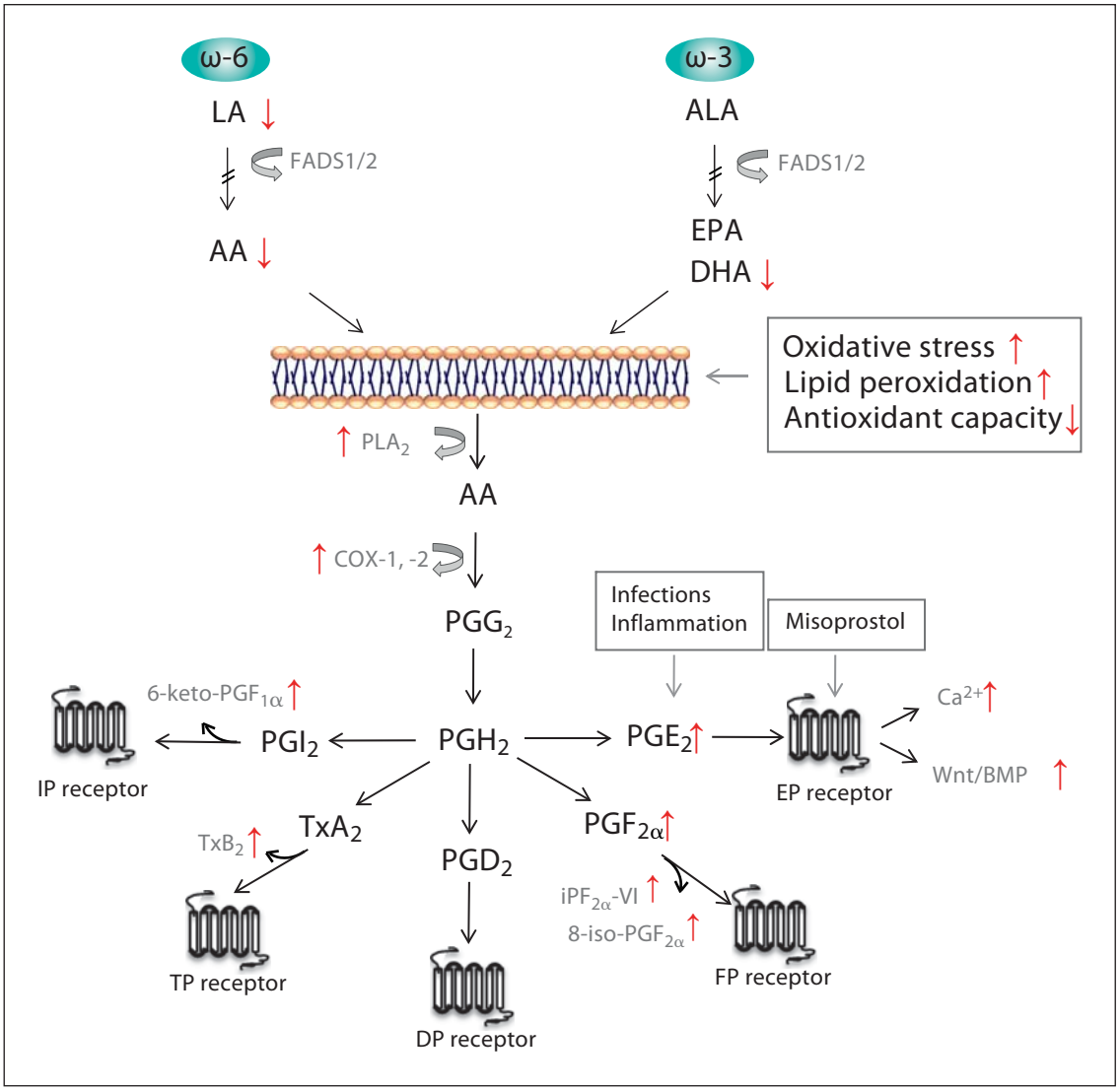

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Fig. 1. Schematic diagram illustrating the most common abnormalities in bioactive lipid signaling pathways associated with ASDs.

9], which together determine the broad severity of autism phenotype.

The emerging evidence implies that abnormal fatty acid metabolism may play a contributing role in the pathology of autism [10–12]. Recent literature suggests that fatty acid homeostasis may be altered in autism as a result of insufficient dietary supplementation, genetic defects, function of enzymes involved in their metabolism, or influence of various environmental agents such as infections, inflammation or drugs. This review provides an overview of the proposed candidate sites along the lipid metabolic pathway that have been implicated in the pathology of ASDs.

Lipid Signaling in the Nervous System

Dry human brain, by weight, is composed of approximately 60% lipids with over 20% polyunsaturated fatty acids (PUFAs) [13–15]. PUFAs, predominantly arachidonic acid (AA, 20:4n-6), eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3), are major components of the neural cell membrane phospholipids. AA and EPA/DHA are derived from two major types of PUFAs, omega-6 linoleic acid (LA; 18:2n-6) and omega-3 α-linolenic acid (ALA; 18:3n-3), respectively [16, 17] (fig. 1). Proper content of omega-3 and ome-

ga-6 fatty acids is important for the integrity and proper functioning of the plasma membrane, such as modulation of ion channels, enzymes and receptor activity [18, 19].

DHA and AA play an important role in the nervous system, including retinal development and vision [20, 21], neurogenesis and neuronal differentiation [22–24], neural plasticity and signal transduction [25, 26], inflammation [27–30], and learning and memory [31–33]. These functions may be regulated by a number of gene products activated by PUFAs during development [34–39]. The plasma membrane phospholipids serve as a supply of second messenger molecules important for normal functioning of the brain [40, 41]. PUFA such as AA or DHA can also be released from membrane phospholipids by the action of phospholipase A_2 (PLA_2) and subsequently metabolized into various types of bioactive prostanoids (fig. 1). Cyclooxygenase-1 enzyme (COX-1), constitutive form, or cyclooxygenase-2 (COX-2), inducible form, converts AA to the unstable PGG_2 intermediate and then to the prostanoid precursor PGH_2, which is further metabolized by the prostaglandin (PG) or thromboxane synthases into the major lipid signaling messengers (eicosanoids) such as PGs (PGE_2, $PGF_2\alpha$, PGD_2, PGI_2), and thromboxane A_2 (TxA_2). The five downstream prostanoids are important signaling molecules that exert their effects through activation of their respective G-protein-coupled receptors called EP (E-prostanoid), FP, DP, IP, and TP receptors [42–44]. The released prostanoids play important roles in normal neural function including sleep induction (PGD_2), spatial learning, synaptic plasticity and long-term potentiation or inflammation (PGE_2) [13, 45]. Of these, PGE_2 has gained a considerable attention recently for its involvement in activity-dependent synaptic plasticity via four receptor subtypes EP1–EP4 [46–48].

It is now evident that the brain proper function relies on a balance between the constant supply of the omega-3 and -6 fatty acids in the blood from dietary PUFAs and the release of their metabolites from membrane phospholipids via activation of PLA_2 and other key downstream enzymes (fig. 1) [31, 35, 49–52]. Therefore, alterations of the fatty acids metabolic pathway may affect proper function of the nervous system. An association between ASDs and abnormalities at various sites of the lipid metabolic pathway has been reported in various studies and is discussed in the following sections.

Dietary Lipid Imbalances in ASDs

During the last trimester of pregnancy and the first 2 years of life, human brain undergoes an immense growth during which unesterified omega-3 and omega-6 fatty acid content of the grey and white matters increase considerably [53, 54]. Because of the increased demand, sufficient supply of the essential PUFAs and proper ratio of AA to DHA particularly during early life is critical for proper development and function of the nervous system [16, 31, 55–59]. Both human and animal studies have correlated the presence of AA and DHA during critical period of development to enhanced visual, cognitive and motor functions [23, 60–63]. A link between imbalances in the AA to DHA composition and abnormalities of fatty acid metabolism have been shown to play a role in the pathology of various psychiatric disorders, including attention deficit hyperactivity disorder, dyslexia, dyspraxia, bipolar disorder and schizophrenia [51, 64–71].

Insufficient dietary intake of PUFA during early development and abnormal lipid metabolism have been shown to occur in ASDs as well. Current literature suggests that altered level of omega-6 fatty acids (i.e. AA) and omega-3 fatty acid (i.e. DHA) may result in an imbalance in the ratio between these PUFAs in the nervous system and potentially contribute to the behavioral outcomes seen in autism. A survey study reported that children who were not breastfed or fed on infant formula not supplemented with PUFAs were significantly more likely to develop autism [72]. Altered level of LA, DHA and AA and significantly higher AA:DHA ratio was reported in the blood samples (plasma and red blood cells) of autism patients compared to the control group [15]. Other studies have reported a significant reduction in AA and DHA levels in the plasma of autistic children compared to the levels in controls [73–75]. Decreased level of DHA and subsequently higher AA:DHA ratio were also detected in the red blood cells of children with regressive autism and Asperger's syndrome compared to typically developing controls [14, 76]. Sliwinski et al. [77] observed an increase in the plasma omega-3 PUFAs, in particular DHA and an increase in the total omega-3 and omega-6 PUFA ratio in high-functioning males with autism compared to healthy controls. Moreover, other lipid biomarkers such as saturated and polyunsaturated very long-chain fatty acid-containing phosphatidyl-ethanolamines and DHA-containing ethanolamine plasmalogens (PlsEtns) were also elevated in the plasma of subjects with autism [78].

The link between altered brain fatty acid metabolism and the occurrence of autism-like behavior has been also

demonstrated in animal models. For example, various studies reported that exposure to environmental agents such as propionic acid (PPA), derived from enteric bacteria or diet, may result in the appearance of autism-like behavior in rodents as a result of altered composition of brain phospholipids [79–81]. Intraventricular infusions of PPA, reduction in total monounsaturated fatty acids, omega-6 fatty acids and PlsEtns, decreased omega-6/omega-3 ratio, and increased level of total saturated fatty acids, which is consistent with reports observed in the blood of autistic patients [79, 82].

Although there are some differences between the reported results, overall these studies show that imbalances in omega-3 and omega-6 fatty acids exist in patients with autism and likely contribute to the behavioral outcomes in some subsets of autistic patients. Interestingly, administration of supplements containing omega-3 and omega-6 fatty acids resulted in increased level of these fatty acids in the blood, reduced AA:DHA ratio and improvements in several behavioral domains such as eye contact, concentration and motor skills in individuals with autism [15]. Supplementation of omega-3 fatty acids has been shown to be effective in ameliorating hyperactivity associated with autism [83]. Moreover, improvements in behavior and significant reduction in the elevated DHA and very long-chain fatty acid biomarker level were observed in autistic subjects taking carnitine supplements [78]. Previous studies have shown that carnitine, normally required for fatty acid metabolism, is significantly reduced in some children with autism [84].

The molecular mechanisms for the altered PUFA level in autistic children are not well understood. Some potential causes have been proposed, including insufficient dietary intake of PUFA precursors, defects associated with enzymes involved in the conversion of dietary PUFAs into longer and highly unsaturated derivatives or deficiency in the process of incorporation of PUFAs into membrane phospholipids [73]. It has been suggested that fatty acid desaturase 1 (FADS1, delta-5-desaturase) and fatty acid desaturase 2 (FADS2, delta-6-desaturase), the rate-limiting enzymes in the metabolism of LA and ALA (precursors of AA and DHA), could contribute to lipid imbalances observed in autism. Interestingly, FADS1 and FADS2 are located in a close proximity to a linkage peak for autism on chromosome 11q22 [85]. This is an appealing possibility since recent studies have found an association between genetic variants in FADS1/FADS2 and attention deficit hyperactivity disorder [86] and other complex diseases, including bipolar disorder or atopic syndrome [87, 88].

Abnormalities in PG Metabolic Pathway Associated with ASDs

Phospholipase A_2

PLA_2 is an enzyme involved in the maintenance of membrane phospholipids. There are three major types of PLA_2 enzyme: the calcium-dependent group IV cytosolic PLA_2, the group II secretory PLA_2 and the group VI calcium-independent PLA_2 [40, 89]. PLA_2 releases AA from the *sn-2* position of phospholipids, a precursor of key lipid mediators such as PGs (fig. 1) [89, 90], and it has been shown to play a key role in neuronal plasticity [91]. Stimulation with various neurotransmitters such as glutamate [92], *N*-methyl-D-aspartic acid [93], or α-amino-3-hydroxy-5-methyl-4-isoxazole PPA [94] can lead to PLA_2 activation and release of AA and its metabolites. Additionally, AA and DHA can be released in the presence of stimuli such as cytokines during the inflammatory response [95].

Elevated level of PLA_2 in red blood cells has been associated with neuropsychiatric disorders such as schizophrenia, depression, bipolar disorder, dyslexia and autism [14, 96]. A substantial amount of evidence has accumulated on elevated plasma levels of PLA_2 in schizophrenia patients compared to healthy controls [14, 97–99]. Three single nucleotide polymorphisms in the gene encoding for cytosolic PLA_2 have been linked to schizophrenia and found to play a possible role in the etiology of this disorder [100–103]. Interestingly, the genes encoding human calcium-independent PLA_2 and secretory PLA_2 map to regions on chromosome 8q23–24 and 7q31, respectively [104, 105], which have been previously linked to autism [106–108]. It has been suggested that the altered levels of AA and DHA in individuals with autism described above may be attributed to abnormalities in PLA_2. Indeed, significantly increased activity of type IV PLA_2 has been reported in red blood cells of patients with autism and Asperger's syndrome compared to the controls, strengthening the hypothesis that abnormal lipid metabolism occurs in autism [14, 109]. It has been proposed that the observed increased PLA_2 activity in individuals with autism may be the cause for elevated breakdown of PUFAs and their subsequent reduced incorporation into membrane phospholipids. Overall, the literature suggests a link between abnormalities in PLA_2 enzymes and some psychiatric disorders including autism spectrum, which substantiates the importance of downstream lipid signaling molecules in the proper functioning of the nervous system.

COX Enzymes

COX is the key enzyme that converts AA to PGs [45] (fig. 1). COX-1 mediates 'housekeeping' functions in most tissues, and COX-2 is the inducible form and participates in the inflammatory responses. Growing evidence shows that COX-2 plays an important role in the nervous system via production of downstream signaling molecules such as PGs [41]. The COX-2/PGE2 pathway plays an important function in synaptic plasticity and refining of mature neuronal connections [110–112] in addition to its role during inflammatory response and oxidative stress [113–115]. It has been shown that selective COX-2 inhibitors can cause a reduction in long-term potentiation, which in turn can be reversed by addition of exogenous PGE_2, but not PGD_2 or $PGF_2\alpha$, indicating an important role for COX-2 and its downstream metabolites in the nervous system [112]. Interestingly, it has been shown that PGE_2 can stimulate glutamate release from astrocytes and modulate the activity of neighboring neurons [116–118].

Altered COX-2 level has been reported in neurological disorders, such as stroke and Alzheimer's disease or psychiatric disorders, indicating that it may contribute to abnormalities in the nervous system [119–122]. The evidence for the involvement of the COX-2/PGE_2 pathway in ASDs is now emerging. COX-2 activity and production of PGs is normally induced by cytokines or proinflammatory molecules [119] and altered immune responses have been reported in cases of ASD [123, 124], suggesting the possible involvement of COX-2 in some cases of autism. More recently, an association between PTGS2 polymorphism (the gene encoding COX-2 enzyme) and ASDs has been reported [125]. Furthermore, altered laminar pattern of COX-2 immunoreactivity in the cortex has been shown in individuals with Rett syndrome, a form of ASD, further strengthening the evidence for the involvement of abnormal COX-2 signaling in the pathology of the autism disorders [126].

PGE_2 Signaling Pathway and Early Development

PGE_2 is a signaling molecule that diffuses rapidly through the membranes and exerts its diverse effects in the nervous system through four G-protein coupled EP receptors: EP1, EP2, EP3 and EP4 [127–129]. The role of PGE_2 in mediating physiologically important functions such as modulation of pain, fever, and inflammatory response in the nervous system is well established [130–135]. In addition, the involvement of PGE_2 signaling in early development including formation of dendritic spines and neuronal plasticity is also emerging [112, 136].

Clinical studies reported that prenatal exposure to the drug misoprostol, a prostaglandin type E analogue, during the first trimester of pregnancy may contribute to neurodevelopmental defects, including Möbius syndrome, a disorder associated with damage to the sixth and seventh cranial nerves, and ASD [137–144]. This indicates that early embryonic exposure to misoprostol may interfere with the PGE_2 signaling and have neurotoxic effects on the developing nervous system. Misoprostol is commonly used as a drug in treating stomach ulcers [145], inducing labor [146] or in medical termination of pregnancy [147]. It has been suggested that the embryo is most vulnerable to misoprostol during early stages of pregnancy, 5–6 weeks after fertilization [148]. Some evidence for the molecular effects of misoprostol action on cell function comes from a recent study on Neuro-2a cells. Misoprostol and PGE_2 can elevate intracellular calcium level and the amplitude of calcium fluctuations in growth cones, as well as reduce the number and length of the neurite extensions in a dose-dependent manner via EP receptors [149, 150]. Interestingly, it has been previously shown that dysfunction in calcium regulation may play a role in the pathogenesis of ASDs [151–157]. These studies suggest that misoprostol may contribute to the neurotoxic effects on neuronal development and communication via PGE_2 pathway.

Various studies have reported a crosstalk between COX-2/PGE_2 signaling pathway and morphogen molecules such as Wnt (wingless) or BMPs (bone morphogenetic proteins) and their cooperative regulation in neuronal differentiation [158–163]. This is interesting because Wnt and BMP signaling normally play a key role in early patterning of the nervous system, neural tube formation, neuronal migration and differentiation, as well as synaptogenesis, synaptic plasticity and synaptic differentiation [164–168]. *Wnt-2*, one of many *wingless* genes regulating cell fate and patterning during early neuronal development [169], is located in the region of chromosome 7q31–33 linked to autism [108, 170, 171]. Interestingly, mutations and polymorphism in *Wnt-2* were found in individuals with autism and severe language abnormalities, respectively, indicating its potential involvement in the pathogenesis of ASDs [172]. Wnt signaling pathways also play an important role in axon guidance and synapse formation, which involves the release of calcium from intracellular stores for growth cone remodeling and synaptogenesis [173]. PGE_2- or misoprostol-induced alteration of calcium fluctuation in growth cones as shown by Tamiji and Crawford [174, 175] may potentially interfere with Wnt signaling pathway and affect differentiation. It has

been shown that Ca^{2+} signaling triggered by neuronal activity mediates synthesis and secretion of CREB-dependent transcription *Wnt-2* and contributes to proper dendritic outgrowth and branching, suggesting the importance of the protein in neuronal development [176]. Moreover, infections associated with the development of gastric cancer can induce the COX-2/PGE_2 signaling pathway by significantly increasing the level of PGE_2 through induction of COX-2 and mPGES-1, membrane-associated PGE synthase-1, and subsequent activation of Wnt and inhibition of BMP signaling pathways [158]. It has also been reported that increased transcription of COX-2 gene and PGE_2 level was induced by Wnt signaling pathway in epithelial cells and cancer stem cells, further strengthening the cooperative interaction between these pathways [160, 163, 177].

The expression of four EP receptors' transcripts (EP1, EP2, EP3β and EP4) significantly increases in the mouse during embryonic day 11–15 (early neurogenesis), indicating that the PGE_2 signaling pathway may have an important role during early development [174]. Many brain structures, such as medulla, pons and cerebellum, start to develop at the early stages of the neurogenesis (embryonic day 12) and others, such as, hippocampus, hypothalamus, thalamus and entorhinal cortex that begin developing at around day 15 [178]. The early brain pathology in many of these regions has been reported in autism [179–181]. A direct involvement of COX-2/PGE_2 signaling pathway in the development of these structures still remains to be established.

Contribution of Oxidative Stress and Lipid Peroxidation in the Etiology of ASDs

Membrane phospholipids are primary targets of oxidative stress, a state in which there is an imbalance between the production of reactive oxygen species and the antioxidant capacity of the cells, including enzymatic and nonenzymatic mechanisms [182]. Reactive oxygen species may induce lipid peroxidation, the oxidative breakdown of lipids, which can disrupt the composition of membrane phospholipids and alter neuronal function [183, 184]. Presence of double bonds in membrane phospholipids makes them particularly susceptible to oxidative damage [185, 186]. The brain is considered vulnerable to oxidative stress particularly during its early development because of high lipid content and limited antioxidant capacity making children more susceptible to insults [187, 188]. Purkinje cells in the cerebellum, for instance, are particularly vulnerable to oxidative stress [189, 190]. Interestingly, significant loss of Purkinje cells accompanied by gliosis was determined in some children with autism [191, 192].

Various studies have reported elevation of lipid peroxidation markers accompanied by a reduction in antioxidant enzymes in individuals with autism, suggesting a contribution of altered lipid signaling to the pathogenesis of the disorder [11, 12, 193, 194]. Glutathione (GSH) is one of the main antioxidants that protect against lipid peroxidation and oxidative stress in the neurons [195]. Lower levels of reduced GSH (active form) during early postnatal life indicate that the developing brain might be more susceptible to oxidative damage [196]. It has been shown that children with autism have lower levels of the reduced form of GSH, and therefore a decreased ratio of GSH to the oxidized form disulfide GSH. Additionally, a deficiency in methionine and cysteine (precursors in the production of GSH) has been detected in these patients, suggesting that they might be more prone to oxidative stress and at a greater risk of developing brain disorders [12, 78, 197–199]. Several polymorphisms affecting methionine and GSH metabolism have also been reported in cases of autism, suggesting a possibility of genetic influences [197, 200].

Interestingly, children with autism exposed to mercury showed significantly decreased level of GSH [201]. Two studies of children in the San Francisco area and Texas found that children living in close proximity to industrial power plant sources of mercury had significantly higher prevalence of autism [202, 203]. Evidence of exposure to mercury due to maternal dental amalgam or vaccination has been also reported in some cases of autism [201]. Pre- or postnatal exposure to toxic metals such as mercury has been shown to contribute to increased oxidative stress and toxic effects on the developing nervous system [204].

Junaid et al. [205] characterized a single nucleotide polymorphism (C419A) in another antioxidant enzyme glyoxalase 1 (Glo1) and showed significantly higher frequency for the A419 allele in patients with autism, suggesting that it might be a predisposing factor in the etiology of the disorder. In addition, a reduced Glo1 enzyme activity has been also reported in the brain of autism subjects [205]. Interestingly, Glo1 is located in close proximity to an autism locus on chromosome 6p identified by linkage and association studies, strengthening a possible involvement of Glo1 in autism [206, 207]. Furthermore, the level of malonyldialdehyde, the end products of lipid peroxidation, as well as antioxidant proteins ce-

ruloplasmin and transferrin, have been shown to be significantly elevated in the plasma or urine samples of autistic children compared to healthy controls [10, 11, 194, 208].

In general, evidence for altered antioxidant capacity and increased oxidative stress in individuals with autism is compelling. Emerging evidence in the recent reports also shows a role played by prostanoid metabolites in the increased oxidative damage in some patients with autism. The levels of a lipid peroxidation biomarker 2,3-dinor-thromboxane (TxB_2), the metabolite of the TxA_2 derived from platelets, and 6-ketoprostaglandin $PGF_1\alpha$ (6-keto-$PGF_1\alpha$), the metabolite of the endothelium prostacyclin (or PGI_2; fig. 1) have been significantly elevated in children with autism [209]. Moreover, 8-isoprostane-$F_2\alpha$ (8-iso-$PGF_2\alpha$) and isoprostane $F_2\alpha$-VI ($iPF_2\alpha$-VI), by-products of prostaglandin $F_2\alpha$ ($PGF_2\alpha$) peroxidation produced in a nonenzymatic oxidation of AA (fig. 1), have also been shown to be significantly higher in red blood cells or urine sample of children with autism compared to the healthy controls [10, 209]. Elevated level of $iPF_2\alpha$ was also found in plasma of children with autism [74] and Rett syndrome patients [210]. The increased accumulation of F_2-isoprostanes, which normally promotes platelet aggregation and vasoconstriction [211], might explain the altered platelet reactivity in children with autism and may contribute to the vascular abnormalities in these patients [212, 213]. Although the effects of the elevated level of PG metabolites in the nervous system need to be elucidated, the reported findings further support the presence of altered lipid biogenesis in ASDs.

Involvement of Immunological Factors

Emerging evidence suggests that immunological factors might have an effect on brain development through modification of COX-2/PG signaling, and play a role in the pathology of some mental disorders [214–217]. COX-derived lipid mediators such as PGE_2 or $PGF_2\alpha$ have been shown to be significantly increased following infections [218–220] or inflammations, especially during pregnancy [221–223]. Several clinical studies and case reports have shown possible contributions of viral infections and abnormal immune response in some cases of autism [224]. It has been shown that prenatal and postnatal infections may trigger autoimmune responses in autism [225–227] or stimulate immune responses in the mother or offspring [228–233].

Prenatal and postnatal exposure to viral infections such as measles [234], rubella [235], herpes viruses [236], and cytomegalovirus [237, 238] has been associated with autism. Moreover, polyomavirus genome was detected in postmortem brain tissues from individuals with autism, indicating the presence of infection in the brain of these patients [239]. Although the molecular mechanisms by which viral infections contribute to the pathology of autism via PGE_2 signaling are still largely unknown and often inconclusive, the animal models provide some indirect evidence that altered immune responses due to infections might contribute to the development of autism. In animal models, pre- and postnatal infections have been shown to lead to immunological changes in offspring, gene alterations in the brain and specific behavioral changes similar to those found in autism spectrum [216, 217, 240–243]. Prenatal exposure of pregnant mice to viral infections also results in increased pyramidal cell density, reduced size of the Purkinje cells of the cerebellum and brain enlargement in the embryos [244]. Similar changes were observed in the brain of individuals with autism [179, 245, 246].

The immune system, including its inflammatory components, is essential in defense against pathogens. Omega-6 and omega-3 PUFA eicosanoids play a central role in regulating immune and inflammatory responses [247, 248]. Eicosanoids derived from omega-6 PUFAs (AA) have proinflammatory and immunoactive role, whereas eicosanoids derived from omega-3 PUFAs (EPA and DHA) have anti-inflammatory properties. PGE_2, the most abundant eicosanoid produced predominantly from AA, induces cytokine expression [249–252]. A number of case studies provide evidence that dysfunction of the immune system such as generation of antibodies or stimulation of cytokine production may result in pathologies of autism [123]. Elevated levels of plasma immunoglobin classes have been reported in some children with autism, indicating altered susceptibility to infections [229, 253, 254]. Production of proinflammatory cytokines such as tumor necrosis factor-α, interleukin-6 and interferon-γ, have been elevated in the blood of autistic children compared to healthy controls [255–261]. Immunocytochemical studies using brain tissues from individuals with autism showed that neuroglia-derived macrophage chemoattractant protein-1 and tumor growth factor-1 were the most prevalent cytokines, indicating that immune dysfunction may result in CNS pathology and contribute to the development of autism [262]. Elevated cytokine production can alter CNS function and development [224]. For example, in cultured rat embryonic

hippocampal neurons interferon-γ inhibits dendritic outgrowths, thereby decreasing synaptic formation [263]. Interestingly, reduced dendritic branching has been shown in the hippocampus of autistic patients [264]. Recent studies indicate that gastrointestinal inflammation can also affect CNS via cytokines and contribute to the development of ASDs [265–267]. In animals, intracerebroventricular injections of PPA (the metabolic end product of enteric bacteria) result in astrogliosis in the brain of the animals, suggesting neuroinflammation as a result of activation of CNS innate immune cells [81]. These models of infection in developing animals provide evidence that viral infections and the resulting immune response may alter neuronal development and lead to behavioral abnormalities seen in autism. Further studies are required to provide a direct link for the effect of immunological factors on the function of the COX-2/PG pathway and their contribution to the pathology of autism.

Conclusions

Autism is a complex neurodevelopmental disorder caused by interaction between genetic and environmental factors. Although autism is behaviorally defined and its biochemical defects are still not well understood, several lines of research support the hypothesis that children with autism show higher rates of in vivo lipid metabolism than healthy controls. The provided evidence shows that impairment at various steps of the lipid metabolic pathways may contribute to the development of autism. These studies collectively suggest that lipid signaling may play an important role in the pre- and postnatal period, and alterations of this pathway can negatively impact the development of the nervous system and lead to autism. Identification of various genetic or environmental factors contributing to deficits in these lipid signaling pathways in individuals with autism will likely be important for understanding the molecular mechanisms of the disorder and the development of novel therapeutic and prevention strategies early in life.

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