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Autistic disorder and phospholipids: A review

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ABSTRACT

Dysregulated phospholipid metabolism has been proposed as an underlying biological component of neurodevelopmental disorders such as autistic disorder (AD) and attention-deficit/hyperactivity disorder (ADHD). This review provides an overview of fatty acid and phospholipid metabolism and evidence for phospholipid dysregulation with reference to the membrane hypothesis of schizophrenia. While there is evidence that phospholipid metabolism is at least impaired in individuals with AD, it has not been established whether phospholipid metabolism is implicated in causal, mechanistic or epiphenomenological models. More research is needed to ascertain whether breastfeeding, and specifically, the administration of colostrum or an adequate substitute can play a preventative role by supplying the neonate with essential fatty acids (EFAs) at a critical juncture in their development. Regarding treatment, further clinical trials of EFA supplementation are essential to determine the efficacy of EFAs in reducing AD symptomatology and whether supplementation can serve as a cost-effective and readily available intervention.

1. Introduction

Autistic disorder (AD) is a lifelong neurodevelopmental disorder that has been growing in prevalence over several decades [1]. AD is now a more prevalent childhood disorder than Type 1 diabetes, Down Syndrome and childhood cancer combined [2]. In the UK, 1% of children aged between 5- and 9-years of age have an existing diagnosis on the autistic spectrum and for every three cases that are diagnosed, there may be a further two cases that remain undiagnosed [3]. These figures represent a twelve-fold increase in AD over the last 30 years [3]. In Australia, prevalence is established at 1 in 160 children [4]; however, this figure is based on data from 2003/2004 and therefore may underestimate current prevalence. Although there is no general agreement as to the reason(s) for this continuing increase in prevalence, with the number of children diagnosed with AD growing, research into the disorder gathers even more urgency and the burden on families, health, education and welfare services ever greater.

For much of its history, AD has been considered a discrete psychological disorder and largely managed with behavioural interventions. However, many studies have outlined the dimensionality of AD in regard to its comorbidity with other neurodevelopmental disorders such as ADHD, dyslexia, dyspraxia [5] and epilepsy [6]. In addition to this, the fact that all of the aforementioned disorders affect a disproportionate number of males than females and that there is a strong familial association has led to a re-conceptionalisation of these disorders [5]. A new proposition is that there may be an underlying biological component that is modified by an individual's genetic constitution and exposure to environmental factors [7]. Researchers are now theorising that one of the underlying biological components in all these neurodevelopmental disorders involves dysregulated phospholipid metabolism [5,8,9].

The brain phospholipids are exceptionally rich in highly unsaturated fatty acids (HUFAs) [10,11] and in contrast to other bodily tissue, a unique feature of neurons is the smaller amounts of the precursors LA(18:2, n-6) and ALA(18:3, n-3) and the higher amounts of their metabolites: AA(20:4, n-6) and DHA(22:6, n-3) [11–13]. The two major PUFAs in all vertebrates are AA and DHA [14] and account for 20% of the dry brain weight [10,15]. Also present in phospholipids are DGLA(20:3, n-6), adrenic acid(22:5, n-6), EPA(20:5, n-3) and DPA(22:5, n-3) but they are not as prolific as AA(20:4, n-6) and DHA [11,12]. DHA is known to be involved in cell signaling and cell proliferation [16] and has an important structural role in the brain [17] whilst AA is crucial for brain growth. EPA(20:5, n-3) seemingly has no structural role, but it is considered vital for the regulation of brain function [17].

Phospholipases are enzymes that break down phospholipids and particular interest is taken in the phospholipases A2 (PLA2) enzymes which are upstream regulators of many inflammatory processes. PLA2 recognizes the Sn2 bond in phospholipids and catalytically hydrolyzes the bond releasing AA(20:4, n-6), EPA(20:5, n-3) and DHA(22:6, n-3) [18]. AA is then modified in

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active compounds called eicosanoids (prostoglandins, leukotrienes and thromboxanes) which are local hormones that participate in a number of physiological as well as pathophysiological conditions such as the activation of immune cells, platelet aggregation and parturition initiation [19]. EPA and DHA are metabolized to resolvins and protectins that have important roles in the resolution of inflammation [18].

Phospholipids are a unique intersection of the environment and genes as the final structure of each phospholipid molecule depends on an interaction between genetic and environmental factors [20]. That is, the enzymes involved in the synthesis and breakdown of phospholipids are under genetic control, but the key essential fatty acids (EFAs) of neuronal phospholipids must come exogenously, from the diet. Strictly speaking, EFAs are solely the precursor fatty acids: LA(18:2 n-6) and ALA(18:3 n-3), however, as the EFAs cannot be synthesized de novo, if they are unavailable they will be replaced by non-essential fatty acids, such as saturated fats, thus changing the phospholipid structure [11]. For example, during dietary deprivation of ALA(18:3 n-3), DHA(22:6, n-3) is replaced by DPA(22:5, n-6) in the retina and brain of animals [21]. As this fatty acid is the most like DHA, this seems to suggest the existence of a compensatory mechanism [21]. Consequently, for the purpose of this review, all the polyunsaturated fatty acids (PUFAs) are referred to as EFAs.

A disruption of membrane phospholipid metabolism was originally proposed by Horrobin et al. [22] as the possible etiological basis of schizophrenia and is known as the membrane hypothesis of schizophrenia. The concept proposes that brain phospholipid metabolism is altered because of an increased rate of loss of DGLA(20:3, n-6), EPA(20:5, n-3), AA(20:4, n-6) and DHA(22:6, n-3) from the Sn2 position of phospholipids. This loss leads to changes in the functioning of the membrane-associated proteins and of the cell signaling systems. One explanation for this is thought to be overactivity of one or more of the PLA2 group of enzymes which remove these EFAs from the Sn2 position.

The evidence put forward for the membrane hypothesis of schizophrenia is as follows:

1. Increased circulating levels of PLA2 enzymes in the blood-stream [23–25].
2. Reduced levels of AA(20:4, n-6) and DHA(22:6, n-3) in red cell membrane phospholipids [26–29], perhaps due to oxidative stress [30].
3. 31-phosphorus neurospectroscopy (^{31}P MRS) indicating an increased rate of phospholipid breakdown in the brain of unmedicated schizophrenics [31,32].
4. A diagnosis of schizophrenia being associated with a reduced flushing response to oral or topical niacin indicating that the amount of available AA(20:4, n-6) is reduced [33].
5. Reduced ERG response to light stimulus [34–36] indicating reduced DHA(22:6, n-3) availability [11,35].
6. Two different genetic abnormalities found on chromosome 1 in the vicinity of the gene for PLA2 [37].
7. Clozapine raising the red cell phospholipid AA and DHA levels in schizophrenic patients [38] and perhaps accounting for some of the therapeutic effects [11].
8. Resistance to arthritis and other inflammatory diseases, resistance to pain and improvement in psychosis which frequently occurs in response to fever [22,39,40].

With evidence mounting that irregular phospholipid metabolism was, at least, concomitant with schizophrenia, research commenced into other neurodevelopmental disorders with the finding that fatty acid deficiencies are also over-represented in attention-deficit/hyperactivity disorder (ADHD), depression, pervasive developmental disorder, developmental coordination disorder and epilepsy [10,41–43].

Further, dysregulated lipid metabolism is now accepted as a pathogenic factor in many neurological disorders such as bipolar disorder and neurodegenerative diseases such as Alzheimer's, Parkinson's, Niemann-Pick and Huntington diseases [18]. Altered lipid metabolism is also believed to be a key event which contributes to central nervous system (CNS) injuries such as stroke [18].

Research into phospholipid in AD is in its infancy and began with the observation that many children with AD have visible signs of fatty acid deficiencies such as excessive thirst, frequent urination, keratosis pilaris on the upper arms or upper thighs, dandruff, and atopic tendencies [43].

2. The evidence for a phospholipid pathogenic component in autism spectrum disorder

2.1. Increased circulating levels of PLA2 enzymes in the bloodstream

Bell et al. [43] identified significantly increased red blood cell type IV PLA2 activity in patients with regressive autism, classical autism and Asperger's disorder which is consistent with previous findings of elevated PLA2 in schizophrenia, depression, bipolar disorder and dyslexia [44]. An unexpected finding was that the HUFA composition of the regressive autism group reduced dramatically by between 60% and 82% following 6 weeks of storage at −20 °C. This unexpected loss of red blood cell PUFAs was also found in a study of schizophrenic patients [45]. At −20 °C, the decay rates of schizophrenic patients' red blood cell PUFAs were nearly twice that of non-patient control participants. Both studies theorized that elevated levels of PLA2 activity may account for the increased degradation [43,45] although Bell et al. also considered a possibility of increased lipid peroxidation in the affected sample.

2.2. Reduced levels of AA and DHA in red cell membrane phospholipids

A study comparing plasma fatty acid levels of children with AD and children with mental retardation and no autism diagnosis found that DHA(22:6, n-3) levels were reduced by 23% in autistic children [10]. AA(20:4, n-6) levels were also lower (but not significantly) and the total PUFA levels were reduced by about 20% in the total plasma of children with autism [10]. A significant increase in the Omega 6/Omega 3 ratio values in children with AD was found. There was also a tendency to reduced levels of EPA(20:5, n-3) but not significantly. It was noted that the children with mental retardation may not serve as a true control given that they also may have fatty acid deficiencies so the differences between groups may have been reduced [10]. In another study, significantly lower levels of AA were found in patients with regressive autism compared to controls [43].

A case study of an 8-year-old male found reduced levels of DHA and EPA, despite a normal blood level of their precursor, ALA(18:3 n-3). Omega-6 fatty acids were at normal levels [46].

Bu et al. [47] were not able to replicate the findings of Bell et al. [43] although a few alterations of red blood cell membrane fatty acids were found in regressive autistic children. Bu et al. did not find an increased ARA(20:4, n-6)/EPA(20:5, n-3) ratio in children with classic or regressive autism. Whilst EPA levels in both classic and regressive autistic groups had wider variations compared to the children with developmental disabilities and the neurotypical control group, the variation was not significant. However, Bu et al. also reported that two PUFAs: eicosenoic acid and erucic acid, were elevated in children with regressive autism compared to the

neurotypical control group. As eicosenoic acid is a saturated fatty acid, the acid in question must be, in fact, eicosadienoic acid (20:2, n-6). Erucic acid (22:1, n-9) is a monounsaturated acid so the elevated level of erucic acid (22:1, n-9) should not be of significance in regard to the membrane phospholipid hypothesis. A significantly higher level of eicosadienoic acid (20:2, n-6) was found in children with regressive autism when compared to the group of children with early onset autism. Bu et al. did not find any evidence that Omega-3 fatty acids were decreased in children with AD.

A larger study of 153 cases of autism and 97 general population controls [48] found an overall trend for those with an autism diagnosis to have lower DHA(22:6, n-3) levels; however, lipid compositions varied sufficiently to overlap with the distributions in the control group. Interestingly, significantly lower levels of AA(20:4, n-6) were found, but only in the females with autism compared with the female controls.

2.3. 31-phosphorus neurospectroscopy (^{31}P MRS) and phospholipid breakdown

In 1993, a pilot study [49] found evidence (albeit described as tentative), for alterations in phospholipid metabolism in eleven high-functioning autistic and adolescent young men after controlling for age and IQ effects.

2.4. Niacin response

Puri and Singh [50] found no significant difference between the mean volumetric niacin response in patients with autism and the mean volumetric niacin response in the control group. They concluded that the fatty acid abnormalities in autism are likely to differ from those that occur in schizophrenia.

2.5. Reduced ERG response

Reduced ERG b-wave amplitude was found in 48% of individuals with AD [51] and four out of six first-degree relatives [52]. ERG responses were altered in a group of autistic children when compared with a normal reference range of responses and the alterations positively correlated with the clinical severity of the autism [53].

2.6. Genetic abnormalities on the PLA2 gene

One case study has reported a genetic site linked to autism on chromosome 8q22 is in the proximity of the gene for secretory soluble PLA2 [54,55]. Given the important role the PLA2 enzyme has in hydrolyzing the sn-2 fatty acids in phospholipids it is theorized that this enzyme may have an important role in the etiology of autism [56].

2.7. Clozapine

A single case study of long-term treatment of autism in an adult male, showed that over a 5-year treatment period with Clozapine, there was a marked improvement in levels of aggressiveness and social interaction [57]. No data exists in regard to the effect of Clozapine on red cell phospholipid PUFA levels in AD, but the possibility exists that some of the improvement in symptomatology may be due to changes in PUFA levels after administration of Clozapine as per the effect in those with schizophrenia reported by Horrobin [11].

2.8. Pain and fever response

A study of pain reactivity in children with autistic disorder, whilst based on parent report, found abnormally low levels of pain reactivity when compared with non-autistic children when matched for age, sex and socio-economic level [58].

Curran et al. [59] conducted a study in response to the anecdotal evidence of AD symptom improvement during fever. When a child's temperature was over or equal to 38.0 °C, fewer abberent behaviours were found on the domains of irritability, hyperactivity, stereotypy and inappropriate speech.

Currently, more investigation is required in order to fully understand any possible eitiological role of phospholipids in AD. Nevertheless, there appears enough evidence to suggest that fatty acid disruptions or deficiencies are at least a predictable biological presence in AD and, as such, warrant urgent and detailed investigation. Horrobin [11] proposed that increasing the availability of EFAs in the diet would improve symptoms in schizophrenia; however, those with the rate of synthesis and incorporation into phospholipids would be reduced in males and those with an excess of oxidants.

3. Does an increased availability of EFAs attenuate AD symptomatology?

Johnson and Hollander [60] supplemented an 11-year-old boy with a history of autism with fish oils containing EPA which was increased over a period of 4 weeks to 540 mg per day. Both his parents and clinician reported a complete resolution of anxiety and agitation after a week on that dosage and improvements continued for 8 months of follow-up. A significant improvement was noted in the patient's quality of life.

Amminger et al. [61] gave 1.5 g per day of Omega-3 EFAs (.84 g EPA, .7 DHA) to seven autistic males (5–17 years) over 6 weeks. A blinded placebo condition ($n=6$) received coconut oil. Children in the Omega-3 condition were found to improve on measures of hyperactivity and stereotypy, each with a large effect size. A non-significant trend towards improvement on hyperactivity was also found. This result is particularly impressive given the short period of supplementation and the very low power of the analyses due to the small sample size. It remains somewhat curious, however, that the researchers chose to use a lipid (coconut oil) as a placebo as it would be reasonable to speculate that such a material would be unlikely to have a purely neutral effect on the subjects' fatty acid metabolism.

Meguid et al. [15] analysed the plasma PUFA levels of 30 autistic children and found that LA, DHA, LNA and AA levels were all significantly lower in the autistic children compared with the control group ($n=30$). However, the mean ratio of AA/DHA was significantly higher in autistic children compared with the control group. Over a 3-month period the clinical group was supplemented with Omega-3 and Omega-6 fatty acids (60 mg DHA, 12 mg GLA, 13 mg EPA and 5 mg AA) and Vitamin E. 66% showed clinical and biochemical improvement. From blood analyses, the supplemented group showed elevated levels of DHA and LA.

Politi et al. [62] studied the effects of Omega-3 (0.93 g EPA and DHA) supplementation in an open label study of 19 young adults (18–40 years old) with severe autism (CARS >40) over a period of 6 weeks. During this period, the researchers also administered 5 mg of Vitamin E to minimize lipid peroxidation. Behaviour was rated using the Rossago Behavioural Checklist and the inter-rater reliability of caregivers was established at or above 90% at baseline. Both problem frequency and average severity scores were obtained at pre-treatment, during-treatment and post-

treatment phases. The clinical group, all residents at a Community Centre for individuals with autism, showed no improvements in the weekly average frequency of problematic events. And, according to the researchers, the fact that the severity of symptoms worsened between the pre-treatment period and the treatment period indicates that their results "fail to convincingly demonstrate a beneficial effect of Omega-3 FA supplementation in a group of young adults with severe autism" (p. 684). However, an examination of the average severity scores shows that in the post-treatment phase, all participants were consistently scoring under their baseline. Given that FA supplementation may take up to 3 months to substantially influence FA deficiencies [17], it may not be appropriate to look for behavioural change immediately upon the institution of a supplementation regime.

4. Is the rate of EFA synthesis sex dependent in AD?

In dyslexia, dyspraxia and attentional disorders without hyperactivity, twice as many males as females are diagnosed [63]. For the more disruptive forms of ADHD and AD the ratio is closer to 5:1 [63]. It is estimated that females, in comparison to males, metabolise fatty acids at a rate of 4:1 [64] seemingly due to the fact that testosterone can inhibit fatty acid synthesis [65]. Oestrogen appears to attenuate fatty acid metabolism issues and the relative lack of oestrogen in males makes them more vulnerable than females to deficiencies in HUFAs [63]. Being male is a well-established risk factor for AD [66].

Wiest et al. [48] theorized that the lower AA(20:4, n-6) concentrations in the autistic females may be due to the differences in how autism arises in males and females or due to dietary factors. It would be pertinent to explore the role of oestrogen in AA metabolism to shed further light on this finding.

5. Oxidative stress and AD

Lipid peroxidation is increased in the plasma of children with autism when compared with their neurotypical siblings [56]. Oxidative stress markers such as reduced levels of glutathione, decreased catalase, abnormal iron and copper levels and increased nitric oxide, have all been found in individuals with an AD diagnosis [56]. A review of oxidative stress in psychiatric disorders found evidence for increased oxidative stress in disorders including autism, mental retardation, Rett's disorder, ADHD and schizophrenia [67]. Oxidative stress is associated with increased lipid peroxidation as PUFAs are particularly vulnerable to peroxidation by oxyradicals [67].

6. Fatty acid intake and neurodevelopment

Individuals with schizophrenia are significantly less likely to have been breastfed than controls [68,69]. The protective effect of breastfeeding may be due to breast milk being a rich source of DGLA, AA, EPA and DHA, which may attenuate any adverse consequences of impaired fatty acid synthesis [11]. As infants, especially pre-term neonates, are not able to convert dietary LA and ALA precursors at an adequate rate to the EFAs important in brain development [70,71], it is crucial that preformed DHA and EPA are supplied by diet.

Prenatally, an increase in Omega-3 rich seafood in the maternal diet during pregnancy has been found to be correlated with optimum outcomes for prosocial behaviour, fine motor, communication and social development scores in children aged from 6 months to 3.5 years of age [72]. A study of postnatal EFA supplementation found that premature infant girls supplemented with a high level of DHA(22:6, n-3) performed better at 18 months of age on the Mental Development Index of the Bayley Scales of Infant Development than their non-supplemented peers [73].

The importance of EFAs to neurodevelopment is highlighted by the findings of Salem et al. [16], who demonstrated that when an adult mammal consumes a diet low in DHA(22:6, n-3) and its Omega-3 precursors, the DHA levels in the nervous system is much less altered than are other DHA levels in other organs. The implication being that once neural development has occurred, DHA is "tenaciously retained" [16, p. 945]. In contrast, animal studies have shown that when Omega-3 fat sources are inadequate during early neural development, levels of brain and retinal DHA decline [16]. This points to the potential for a critical window when EFA status needs to be consolidated to ensure adequate levels in the infant.

7. Is a lack of breastfeeding a risk factor for AD?

Schultz et al. [74] surveyed 861 parents of children with AD and 123 parents of children without AD, and found that the children with AD were significantly less likely to have been breastfed. The absence of breastfeeding significantly increased the odds of a later AD diagnosis (OR 2.48, 95% CI 1.42, 4.35). The apparent link between AD and breastfeeding was first cogently addressed by Tanoue and Oda [75], who found that a significant number of infants subsequently diagnosed with an AD had been weaned within 1 week of the commencement of breastfeeding with the duration of breastfeeding proposed as a protective factor. Similarly, the odds of being diagnosed with AD also reduced with the duration of breastfeeding in the Schultz et al. study, but not significantly. One major limitation of both of these studies is that colostrum intake was not accounted for as colostrum contains twice the PUFAs as transitional and mature milk [76]. At this stage, only in animal research is the importance of early fatty acid consumption in the form of colostrum acknowledged and accepted. A study of neonatal calves found that delaying their colostral intake by just 24 h impaired their fatty acid, carotene, retinol and alpha-tocopherol status [77] at least for the first week of life.

8. Conclusion

A review of the literature suggests that there is compelling evidence that phospholipid metabolism is at least impaired in individuals with AD. However, at this stage, it has not been established whether phospholipid metabolism is implicated in causal, mechanistic or epiphenomenological models. More research is needed to ascertain whether breastfeeding, and specifically, the administration of colostrum or an adequate substitute can play a preventative role by supplying the neonate with EFAs at a critical juncture in their development.

In regard to treatment, further clinical trials of EFA supplementation are essential to, at worst, eliminate the possibility of the efficacy of EFAs in reducing AD symptomatology and at best, determine whether supplementation can serve as a cost-effective and readily available intervention. If so, it is critical to determine which EFAs are most effective and in what ratios.

New non-invasive tests such as the measurement of volatiles in breath [78] need to be rigorously applied to investigate the possibility of establishing a reliable biological diagnostic determinant of AD.

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