

Phospholipid Spectrum Disorders in Autism

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What is a “phospholipid spectrum disorder” and why is it relevant to the complex biochemical and physiological abnormalities that occur in autism? Phospholipids are the building blocks of all cell membranes. They provide a barrier between the outside of a cell and the inside thereby preventing mixing of intracellular and extracellular components. As well as containing phospholipids cell membranes contain numerous proteins, including ion channels, receptors and enzymes, many of which have essential roles in cell-cell communication. Such functions are, of course, vital in neural tissues. The structure and function of these membrane-associated proteins can be directly affected by the nature of the phospholipids which surround them. The phospholipids comprise two fatty acids and a polar head group, which can be an amine, amino acid or sugar, attached to a glycerol backbone (**Fig. 1**). The fatty acid components have many roles in determining the structure and function of the membrane and it is the metabolism of these fatty acids which appears abnormal in autistic spectrum disorders (ASD). Fatty acids in cell membranes are subject to natural wear and tear and the damaged ones are removed from the phospholipid by a phospholipase enzyme. The incomplete phospholipid, called a lyso-phospholipid, is damaging to the integrity of the membrane and is normally rapidly repaired by a fatty acyl transferase/ligase enzyme. Therefore, if the phospholipase is overactive, or present at abnormally high levels, and/or the fatty acyl transferase/ligase is under active, then damage to cell membranes will result making them “leaky” and affecting the function of proteins embedded in the membrane. In autism, red blood cell membrane phospholipids have been shown to be abnormally unstable upon storage suggesting that turnover of fatty acids in these membranes may be unusually high. In Aspergers syndrome, although the cell membranes appear more stable, the fatty acid compositions show important differences in terms of their polyunsaturated fatty acid (PUFA) content. Studies in our laboratory indicate that the n-6 PUFA, arachidonic acid (ARA) is often elevated whereas the n-3 PUFAs eicosapentaenoic acid (EPA) and

docosahexaenoic acid (DHA) are often depleted compared to control samples. In addition, using an assay developed by Dr David Horrobin of Laxdale Ltd. biochemists at the Victoria Hospital in Glasgow have shown an increase in the phospholipase A₂ (PLA₂) enzyme in blood cells from individuals with autism and Aspergers syndrome. The PLA₂ releases PUFA, such as EPA, DHA and ARA, from cell membranes resulting in membrane damage and the production of highly inflammatory substances known as prostaglandins, leukotrienes and thromboxanes, known collectively as eicosanoids.

How can abnormal PLA₂ and excessive eicosanoid production result in the physiological and psychological problems found in ASD? The cells of the neural system contain high levels of PUFA representing between 15-30% of neural tissue by dry weight and, of those, ARA and DHA represent 80-90% of the total. In normal synaptic function, ARA and DHA are released into the synaptic junction, by the action of PLA₂, along with neurotransmitter compounds, followed by re-uptake of neurotransmitter and PUFA. If PLA₂ activity is elevated, an excess of PUFA may be released from the synapse resulting in oxidation of the free PUFA. Oxidised PUFA can set up a cascade of reactions resulting in extensive inflammatory reactions and cellular damage.

In the cells of the gut epithelium and endothelium ARA is the predominant PUFA and n-3 PUFA are only minor components. If elevated PLA₂ is present in these cells, free ARA will be produced and a range of highly inflammatory eicosanoids produced. In addition lyso-phospholipids, which remain after phospholipase action, are potent cytolytic agents (that cause cell membrane breakdown) that may cause "leakiness" in gut cells.

The cells of the immune system, including lymphocytes, macrophages and eosinophils, require PLA₂ to produce prostaglandins and leukotrienes essential for enabling immune cells to locate and destroy pathogenic organisms. While low levels of prostaglandins, particularly PGE₂, are stimulatory to the immune system, high levels tend to reduce immune responses. Thus, increased PLA₂ could result in immune suppression as well as increasing the prevalence of auto-immune disorders such as asthma, eczema, rheumatoid arthritis and diabetes.

Work in our laboratory, using red blood cells (RBC) as a model system, has suggested that PLA₂ is elevated in individuals with autism and Aspergers syndrome. The RBC usually contain

less EPA and DHA and, sometimes, more ARA than control subjects. In addition, the RBC membrane PUFA composition appears particularly unstable on storage at -20°C in patients with autism, compared to control subjects. This is strongly indicative of increased PLA₂ in the RBC, perhaps coupled with increased oxidation of PUFA. Recently, in conjunction with the Victoria Hospital in Glasgow and Laxdale Ltd, increased PLA₂ has been confirmed in a number of individuals with autism and Aspergers syndrome. Although we have looked at relatively few (seven) individuals so far all have shown evidence of a phospholipid spectrum disorder. We hope to study these effects in a wider sample of patients with ASD in the near future.

Having identified increased PLA₂ and membrane PUFA loss what steps can we take to alleviate the damage and so improve the well being of individuals with ASD? In schizophrenic patients, where a similar phospholipid disorder has been identified, considerable success has been achieved by supplementation with omega-3 (n-3) PUFA, particularly EPA. EPA is an inhibitor of PLA₂ activity and probably helps to stabilise cell membranes and reduce inflammatory reactions by competing with ARA and modulating the effects of ARA-derived eicosanoids. Although no clinical trials of EPA-rich oils and concentrates have been performed in patients with autism to date, a number of positive reports have been received from parents supplementing their children with EPA preparations. Improvements include improved eye contact and sociability, improved spontaneous speech and improved gut function as well as reduced fluid intake and urination. An EPA intake of around 1-2 g per day seems to be appropriate as provided by concentrates such as Kirunal™ and Eye Q™. It is hoped that a clinical trial of the 97% EPA concentrate produced by Laxdale Ltd., presently being investigated with schizophrenic patients, will be conducted with ASD patients in the near future.

Sources of fish oil supplements

Eye Q™; www.equazen.com or from Boots and Tesco

Kirunal™; www.fincastle.com or the Schizophrenia Association.

EPA fish oil, Holland and Barrett or any fish oil sold under the MaxEPA trade name.

Dosage should be 3 g/day for 3 months then reduced to 2 g/day thereafter.

Fig. 1

