The Neurobiology of Lipids in Autistic Spectrum Disorder

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Introduction

The biochemical complexity of Autistic Spectrum Disorder (ASD) has led us towards an in depth exploration of its systemic presentation from a cellular perspective. Previous examination of patients with ASD have revealed immune insult with an autoimmune presentation.[1-23] Through the efforts of Wakefield[24] at the Royal Free Hospital in London, gut biopsy and ongoing clinical trials have also suggested viral involvement of ASD with positive staining for measles in lymphoid follicles from measles vaccination. Wakefield has hypothesized that there may be a viral interaction between measles vaccination and exposure to chicken pox that initiates the immune derangement in ASD. Protocols for treatment of GI disturbance were limited until Borody[25] applied the work of Tvede and Rask-Madsen[26] with the oral application of bacterial strains such as non-toxigenic avirulent strain of Clostridium Difficile (sixteen strains of bacteria in all were utilized) with cessation of major symptoms in five children (to date) with autism.

Renowned microbiologist Dr. Sidney Feingold[27] has identified at least 12 genus of anaerobic bacterial species missing in four autistic children (hundreds of culture plates were run for this determination) in contrast to controls (forthcoming publication) after a lay facilitator, Ellen Bolte,[28] proposed the connection between tetanus vaccination (clostridium tetani) and autism. The hypothesis forming in regard to autism and clostridium is that neurotoxins are being formed through the immune/gut/CNS axis creating the stereotypic behavior (actually hallucinogenic in nature) exhibited in autistic spectrum disorder. The use of potent antibiotics and therapeutic use of probiotics has not adequately addressed ASD. Borody's approach is to sterilize the gut with potent antibiotics and re-implant the proper balance of all bacteria (including those we consider to be pathogenic). Oral application of bacteria (rather than rectal implantation) may be utilized if the gut is sterilized and medicines (i.e Prilosec) are used to suppress acid formation. This may permit the bacteria to pass undisturbed through the GI tract. Efficacy of this therapy in the gut and brain have recently been observed.

Opiate-like Peptides in Autism

The concept of opiate-like peptides affecting children with ASD was developed by Shattock,[29-30] Reichelt,[31-32] and others[33-34] through examination of urinary metabolites containing peptides from gluten and casein. The opiate antagonist naltrexone proved unsuccessful in controlled trials[35-39] with dietary removal of gluten and casein yielding anecdotal positive results. Association with ASD and serotonin was scrutinized in intricate detail[40-43] but not clarified until Matson[44] (1996, unpublished data) isolated bufotinines, methylated serotonin compounds, in the serum of children with ASD. Matson found that these compounds may be created by the patient evoking hallucinogenic symptoms, and found that children with ASD overmethylate. Friedman[45] (stated in public forum) noted analysis by tandem mass spectrophotometry that aberrant peptides originally derived from casein/gluten as well as Clostridium created hallucinogenic effects initially linking casein ingestion to cellular surface immune response, specifically CD26, which is crucial to clearing of beta-casomorphin. Friedman continued his research (study submitted for publication) linking the effect of opiates from gluten,

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casein, and particular species of Clostridium upon the suppression the enzyme Dipeptidyl Peptidase-DPP4 or CD26 ultimately impacting the liver, kidney, small intestine and blood brain barrier where this enzyme predominates.

The role of CD26 is primarily one of T cell activation, and the cleavage of peptides at the location of proline and alanine thereby breaking down aberrant peptides or inactivation of neuropeptides. Friedman has noted that the amino acid sequencing of peptides in the urine of children contain D-alanine and D-proline isomers, and CD26 cleavage of these isomers is 1000 fold greater than peptides containing the L-isomers of these amino acids. The research of Friedman and Matson link endogenous polypeptides to autistic behaviors (hallucinogenic in nature). Matson's research is oriented to serum rather than urinary metabolites, and suggests that the endogenous creation of bufotinines may be related to bizarre behavioral patterns.

Treatment Protocols

In designing therapeutic treatment strategies, clinicians must consider the following significance factors in the pathogensis of ASD: passage of peptides through the blood brain barrier; electrolyte instability; allergic manifestation; GI disturbance and intestinal permeability.[46] All these markers are indicative of a loss of cell membrane integrity. Bauman[47] and Minshew[48-49] have clearly identified aberrations in neurons and membrane phospholipids in ASD patients. Certainly the removal of casein and gluten may be of tremendous benefit, but metabolic entropy, immune dysregulation and loss of cell membrane integrity must be addressed to sustain the health of multiple body systems.

Information on the use of secretin for ASD has exploded in the press and parents have demanded this treatment, even in the absence of proper scientific investigation such as clinical trials. Understandably, the success of secretin therapy has been mixed, where secretin has evoked speech in some while in others the results have led to autoimmune responses and seizures. The metabolic effects of secretin are that it stimulates the arachidonic acid cascade (contraindicated in seizure disorders), and bicarbonate production. This state will burn off (beta oxidize) fatty acids (including both essential fats, insulating fatty acids and very long chain fatty acids), and increase the metabolism of bile acids. Secretin may also stimulate cholecystokinin-B (CCK-B), which plays a neuromodulatory role in GABA-ergic neurons which may be involved in speech production. Wilson[50] reports stimulation of speech at the time of administration of secretin with the use of provocative neutralization technique, therefore full doses or repeated infusions may be unnecessary. Infusions of secretin will correct the acidosis that most children with ASD present with ultimately impacting hyper-ammonemic (bicarbonate plus ammonia yields urea) states that may be stabilized with an increase in bicarbonate production. Perhaps one should consider oral repletion of bicarbonates as a less invasive intervention.

Each of the biochemical aberrations isolated in children with ASD demand that we examine the cell membrane integrity (including the blood brain barrier), membrane traffic (electrolyte stability and blood gases), the peptide-lipid membrane, nitrogen retention, and the very essence of the communication in the body, the prostaglandins.

Children with ASD present with hepatic, gastrointestinal, renal, immune, endocrine and CNS disturbances which reflect striking metabolic derangement. This is most clearly revealed in examination of red cell lipids (representing four months of cellular metabolism), and show the accumulation of very long chain fatty acids (VLCFAs) indicative of suppressed peroxisomal beta oxidation.

Peroxisomes are organelles within cells which are pivotal in the biotransformation of endogenous compounds in lipid metabolism such as fatty acids, steroids, prostaglandins, the formation of myelin, neurotransmission, and detoxification of exogenous compounds and xenobiotics.[51-52] The accumulation of VLCFAs inside the cell membrane represents defects in peroxisomal beta oxidation.[53] This condition may be used to profile the deleterious effects characteristic of autistic spectrum disorder on the brain, endocrine, gastrointestinal and immune systems, and hepatic cytochrome P450 derangement (involving nitric oxide synthase) due to auto-immune[54] presentation. Therefore, the toxic aspect so often described in autism may be defined clearly through examination of RBC lipids with elevation of VLCFAs a reflection of blocked detoxification mechanisms.

Cellular Interactions and Treatment

Presently, physicians struggle to understand which antioxidants, detoxification methods, hormonal support or pro-oxidant therapies are appropriate in treating ASD. This dilemma can now be clarified through new understanding of cellular organelle interactions. Tremendous attention has been directed to the mitochondria (energy producing organelle) yet the most important organelle in regard to lipid metabolism and detoxification is the peroxisome.

Peroxisomes are present in virtually all cells but are most prevalent in the liver and kidney where they play a critical role of cellular lipid metabolism and biosynthesis of fatty acids (via beta oxidation). This process involves important physiological substrates for VLCFAs, dicarboxylic fatty acids, prostaglandins, thromboxanes, leukotrienes, pristanic acid, DHCA, THCA and xenobiotics. Individuals with immune, CNS and endocrine disorders often present with complex xenobiotics indicating disturbances in the cytochrome P450 superfamily, a state which parallels disturbances in peroxisomal function. The cytochrome P450s are responsible for the biotransformation of fatty acids, steroids, prostaglandins, leukotrienes and vitamins, as well as the detoxification of exogenous compounds. This process may result in substantial alterations of P450s as xenobiotics may turn off or greatly reduce the expression of constitutive isoenzymes.

Inappropriate use of antioxidants inhibit the beta oxidation or burning of cellular fatty acids and suppress normal lipid metabolism. Large doses of vitamin E, for example, will inhibit tumor shrinkage as beta oxidation is suppressed. Thus potent antioxidants are contraindicated in toxic states (i.e. in the buildup of VLCFAs). The administration of DHEA, pregnenolone, or thyroid hormone stimulates the beta-oxidation of VLCFAs as would pro-oxidant nutrients and oxidative therapies. Children with ASD most often present with acidosis,[54] low CO_2/Bicarbonate[54] and low oxygen.[54,55] Stimulating beta oxidation, however, concurrently stimulates the burning off of essential fatty acids (EFAs), thus it is crucial that the delicate balance of controlling redox potential, beta oxidation, and the administration of essential substrates (lipids, proteins) and catalysts (vitamins, minerals) be utilized specific to the individual child with ASD.

There is now an large body of evidence that suggests that essential fatty acids play a fundamental role in the brain, cell to cell interactions and genetic expression. Understanding lipid and EFA metabolism is crucial for maintaining both physical and mental health. New research on targeted lipid manipulation has shown that dietary changes can dramatically influence the body, and most profoundly, the brain. [62]

Viewing the brain of the child with ASD as a biological orchestration as it relates and interacts with membrane lipids offers a new understanding of the specificity of disturbances within the brain in regard to lipids/peptide interactions on a

cellular level and the intricate integration of essential fatty acids and prostaglandins.

Although the CNS cannot be controlled without attention paid to lipid substrates, fatty acid metabolism has been poorly understood and often is simply ignored in treatment protocols. Proper evaluation and attenuation of lipid metabolism in ASD can provide a powerful therapeutic tool that integrates the CNS, immune, endocrine, hepatic, renal, gastrointestinal, pulmonary and cardiovascular systems.

Red Cell Lipid Analyses Findings

Examination of over 700 red cell lipid analyses[54] of children with ASD have revealed the following characteristic patterns: elevation of VLCFAs (erucic, lignoceric, lumequic, behenic, adrenic, pentacosanoic acids); depression of myelination markers (as the DMA phospholipids); suppression of PG_1 synthesis (ASD patients respond to clonidine and pentoxifilline due to stimulus to PG_1,[56-59]); elevation of the arachidonic acid cascade/PG_2 synthesis;[60] and autoimmune derangement (with elevation of EPA/DHA characteristic of disturbances in cytochrome p450 enzymes, Nitric Oxide Synthase (NOS) and peroxisomal dysfunction.[54] NOS and Nitric oxide (NO) formation is augmented by supplementation of DHA in marine oils.

The autoimmune presentation of ASD may initially respond negatively to marine oils, DHA or flax oil due to both the competitive inhibition of omega 3s to omega 6s (PG_1 series prostaglandins appear to be suppressed[54] in children with ASD) and the stimulation of NOS/NO towards the autoimmune process. Nitric oxide is the smallest biologic product of the human cell and is intimately involved in synaptic plasticity, immunity, neurotransmission, electrolytic stability, vascular regulation, neuromodulation, gastrointestinal and hepatic function. Imbalance of lipid substrates or inhibition of prostaglandin synthesis pathways due to immune insult may create complex immune-CNS interactions that are caused by disturbances within cell membrane dysfunction. Omega 6 essential fatty acids (in this case the precursor PG_1 as evening primrose oil) must be repleted and stabilized before omega 3 supplementation commences.

Consider carefully that the synthesis of prostaglandins is an oxidative process, therefore loading with antioxidants or the incorrect sequence of EFA repletion may impede progress in ASD therapy. Complex nitrogen metabolism is apparent in children with seizures, developmental delay and ASD and involves not only Nitric Oxide, but nitrogen retention as a whole (first described by Mary Coleman[61] as "purine autism").

Patients presenting with suppression of CO_2 may shun nitrogen (protein) rich foods which form ammonia (hyperammonemia). Although buffers and butyrates attenuate abnormal nitrogen metabolism, children with ASD are unique in their presentations. As we examine nitrogen retention/NO, electrolyte stability, catalysts, lipid status we see disturbances in metabolism which require that we use integrative therapies developed from a cellular perspective.

Conclusion

Previously, researchers studying autism were hindered by a lack of medical literature on the importance of essential fatty acids in health and the different physiological effects of their trans and cis isomers. This situation resulted in misinformation among practitioners in regard to appropriate protocols for lipid manipulation. Intractable disorders such as adrenoleukodystrophy (ALD) have brought clarification to the labyrinth of lipid pathways, as separate fatty acids are studied and manipulated through lipid (drug) therapy and other systemic interventions. Medicine has been slow to acknowledge the crucial lipid requirements (4 to 1 ratio of omega 6 to omega 3 or

SR3 by Yehuda[62]) to address neurological degeneration, and now that the data is emerging, it is difficult to extrapolate and utilize it towards successful therapeutic applications.

By studying the research data and isolating individual fatty acids in red cells we can now examine the intricate circuitry of the fatty acid derived prostaglandins, stabilize cell membrane integrity, and for the first time establish lipid treatment protocols with a greater understanding of the brain through red cell membrane dynamics. This may finally open a gateway into resolving autism and many of the neurodegenerative disorders of our time.

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