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A meta-analysis of blood fatty acids in people with learning disorders with particular interest in arachidonic acid ☆, ☆☆, ★

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ABSTRACT

Small individual studies report that people with learning disorders have lower than normal blood concentrations of docosahexaenoic acid and arachidonic acid. The origin and consequence of the subnormal docosahexaenoic acid have been much speculated. However, relatively little attention has been paid to the significance of the low arachidonic acid concentration. Studies were identified through a literature search including subjects with various learning disorders or symptoms thereof and age-matched controls. A meta-analysis of pooled data from the red blood cell and plasma/serum showed that red blood cell arachidonic acid and docosahexanoic acid concentrations were significantly lower than normal [−3.93 and −18.92, respectively (weighted mean difference as a % of weighted mean control)]. Plasma/serum arachidonic acid and docosahexaenoic acid concentrations were also significantly lower than normal [−6.99 and −15.66, respectively (weighted mean difference as a % of weighted mean control)]. However, in absolute amounts the arachidonic acid was as severely depressed as docosahexanoic acid within red blood cells 0.57 mg/100 mg of fatty acid below normal verses 0.59 mg/100 mg for docosahexaenoic acid. Plasma/serum arachidonic acid was even lower; 0.71 mg/100 mg of fatty acid below normal verses 0.34 mg/100 mg for docosahexaenoic acid. The origin, consequences and relative importance of subnormal arachidonic acid to brain function bears further investigation.

1. Introduction

During the last two decades over a dozen published population studies have shown that people with learning disorders including attention deficit hyperactivity disorder (ADHD), dyslexia and autism either have signs of essential fatty acid (EFA) deficiency including dry skin, hair and nails, and frequent thirst and urination [1–3] or they have lower than normal blood concentrations of docosahexaenoic acid (DHA) and to a lesser extent arachidonic acid (AA) based on area % measurements [4–14]. There has been much speculation pertaining to how and why the DHA concentration is lower than normal and the physiological consequence of this [7,15] and lower than normal omega-3 fatty acids in general on brain function [16–18]. However, relatively less attention has been paid to the significance of the low AA concentration.

DHA and AA are highly concentrated in membrane phospholipids of the retina and brain, where they accumulate rapidly during fetal and infant growth spurts and are critical for their structure and function during development [17,19]. These long chain polyunsaturated fatty acids (LC-PUFAs) can influence membrane microstructure and fluidity, recovery from injury, gene expression, cell signaling [19] and immunologic regulation [20]. DHA is the main structural fatty acid in the brain and may impact signal transduction through its effects on ion channels, response to neurotransmitters [21], and formation of second messengers [22]. It may also protect against loss of scaffolding proteins [23,24] and lipid peroxidation [25,26]. However, its functional role is less well elucidated than that of AA [17], the later reported to be involved in the most elaborate signaling system facing neurobiologists [27]. Briefly, stimulated membrane release of neuronal phospholipid AA is achieved through neurotransmitters, neuromodulators and neurohormones. The resulting free AA may directly affect the activity of ion channels and protein kinases within the cell or it may be transformed into a multitude of messenger molecules including eicosanoids, epoxyeicosatrienoic

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acids and endocannabinoids [27] with intracellular as well as extracellular targets. The endocannabinoids that modulate neurotransmitter release may impact on a host of physiological functions including appetite control, energy metabolism, pain perception, memory and learning [28].

DHA and AA are synthesized within the body from dietary alpha-linolenic acid (ALA) and linoleic acid (LA), respectively, through an alternating series of desaturations and elongations [29,30]. However, this process is extremely inefficient with only about 0.1% of the substrates being converted to either DHA or AA in normal healthy adults eating a typical Westernized diet [29]. At least four studies have reported little difference in nutrient intake between controls and children with ADHD [7,13,31,53]. Consequently, abnormalities in DHA and AA concentrations in people with learning disorders are thought instead to arise from a combination of factors including altered enzyme activity affecting conversion of precursor fatty acids and/or excessive utilization of these metabolites [15].

Dietary sources of DHA and AA include fish, meat and eggs, but the daily intake of these nutrients is exceeding small in comparison to that for LA and ALA in adults (Table 1) [32–49] and in children (Table 2) [50–56] in Westernized countries. Dietary recommendations for DHA from post-conception through to adulthood [57,58] are well established while those for AA only exist for preterm and term infants [59,60] and preschoolers according to the Belgian Health Council recommendations [51]. Although, it is generally assumed that excessive LA intake ensures more than enough AA for normal physiological function [61], there are no reference values for this assumption particularly with respect to mental function beyond infancy.

It is believed that within body tissues, DHA status fluctuates quite readily with dietary changes while AA concentrations remain relatively stable and that there is little difference in AA content amongst individuals [18]. Therefore, the occurrence of a subnormal AA concentration in people with learning disorders may be of particular importance to investigate since a deficiency may be physiologically relevant to abnormal brain function.

This investigation includes a meta-analysis of red blood cell (RBC) and plasma/serum (P/S) fatty acid profiles in people with learning disorders relative to normal controls to determine if AA in particular is significantly below normal and the degree of heterogeneity that exits. A critical comparison of DHA and AA blood concentrations and their relative dietary availability against reported dietary requirements of these two nutrients during various stages of development and for physiological function and body composition, coupled with consideration of recently identified polymorphisms in genes related to fatty acid metabolism and results of clinical trials demonstrating successful combinations of fatty acid treatments for subsets of learning disorder patients, highlight areas where additional research is required.

2. Patients and methods

2.1. Literature Search

Published reports written in English including subjects with various learning disorders were identified through a systematic literature search back to 1980 conducted at 2 weeks intervals over an 18 months period up to 31 July 2007 by Nerac Inc., Tolland, USA, a contract research company providing custom research, analysis and advisory services. Broad search criteria were used including Arachidon?, Borag$, Borage, DGLA, Gammalinolen?, Gamma-linolen?, Gamma linolen?, Docosahexaen?, Eicosanoid?, Eicosapentaeno?, Fatty Acid$, Fatty-Acid$, Evening primrose, Fish-oil$, Fish oil$, Linole?, Polyeno?, Polyunsaturate?, Icosapentaeno?, PUFA$, Omega3, Omega-3, Omega 3, Omega6, Omgea-6, and Omega 6, and numerous databases were accessed including Embase, Life Sciences Collection, Food Science & Technology Abstracts, CAB Abstracts, MEDLINE and Biological Abstracts. An additional search on Medline was completed utilizing more specific search criteria including docosahexaenoic acid or DHA or arachidonic acid or AA and learning disorders or attention deficit hyperactivity disorder or dyslexia, reference lists were examined and experts in the field were contacted.

2.2. Subjects

The meta-analysis inclusion criteria was published human observation or intervention trials including subjects with dyslexia, dyspraxia, attention deficit hyperactivity disorder, autism, Asperger's Syndrome, developmental co-ordination disorder, hyperactivity, maladjusted behavior, or symptoms thereof and age-matched controls, that included RBC and/or plasma and/or serum fatty acid profiles. The exclusion criteria was a reported high consumption of oily fish (regularly more than twice per week) or use of fatty acid supplements.

2.3. Data collection

RBC and P/S concentrations of AA and DHA for the patients and controls were extracted from each study and pooled for statistical analysis.

2.4. Statistical analysis

Four meta-analyses were performed: AA and DHA as percent of total fatty acids (subject minus control) in each of RBC and P/S. Both fixed and random effects models were fit, with the assumption of normality of mean differences. Inverse variance weighting was used for fixed effects and DerSimonian–Laird for random effects, when estimating the weighted mean difference. The latter estimates were used when significant heterogeneity was found among the studies, using the χ^2 test.

3. Results

3.1. Literature search outcome

The number of available studies and their subjects was small (Table 3). Although the inclusion criteria specified use of age matched controls, it was decided to include studies that did not satisfy this requirement because the actual ages of subjects and controls enrolled in the applicable studies were not substantially different. Fatty acid data were presented as μg/mL, area %, % of total fatty acids, mg/100 g of fatty acid, weight % of total fatty acids or unspecified. Therefore, all data were converted to % of total fatty acids for comparison. Lipid fractions reported included RBC total lipids, RBC phospholipids, serum phospholipids, plasma phospholipids and plasma total lipids. Plasma and serum data were combined to increase *n*. Methods of statistical analysis also varied between studies and included Kruskal–Wallis [4,6,13], two-sample *t* [10,13], MannWhitney [11] and unspecified [5,7–9,12,14].

Two years had passed since completion of the literature search and meta-analysis, and start of this manuscript preparation. Therefore, it was deemed appropriate to identify any studies published subsequent to July 2007 that contained RBC and/or P/S fatty acid data for people with learning disorders and discuss their results relative to those reported in this publication. Eight studies