

(n-6) and (n-3) Polyunsaturated Fatty Acids and the Aging Brain: Food for Thought¹⁻³

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Abstract

Over the last decade, the role of dietary PUFA in growth, development, and cognitive function in the infant has been a topic at numerous national and international meetings. Only recently has the role of PUFA been more seriously examined as they relate to the aging brain. In fact, a search of the literature reveals very few randomized control trials exploring this research area. However, the literature reveals growing mechanistic evidence that cognitive function of the aging brain can be preserved, or loss of function can be diminished with docosahexaenoic acid, a long-chain (n-3) PUFA. Furthermore, no symposia have taken a serious look at the impact of (n-6) PUFA on the brain, in particular arachidonic acid (AA), the most highly concentrated (n-6) PUFA in the brain. This symposium explores the role of AA metabolism in the brain as it relates to neurological mood disorders. To that end, this symposium was designed to highlight the potential effects of dietary PUFA on the adult brain, an important issue given the growing elderly population in this country and the growing problems with neurological disorders (dementia, Alzheimer disease, Parkinson disease, bipolar disorders, etc.). J. Nutr. 138: 2521–2522, 2008.

Introduction

The impact of neurodegenerative diseases on health and well-being in the elderly is a growing problem with devastating effects for the individuals afflicted, their families, and society in general. The financial and emotional tolls these diseases take on all those affected are difficult to bear. Only now are we beginning to learn how diet can impact mental well-being and that many nutrients are now believed to be involved. It is becoming increasingly evident that long-chain PUFA from the (n-3) family appear to be neuroprotective and that long-chain PUFA from the (n-6) family may also have unique properties in affecting neurobiology.

Docosahexaenoic acid in the aging brain

There appears to be a growing literature on the importance of PUFA in brain function (1,2). A preponderance of this research has focused on docosahexaenoic acid (DHA),⁴ a PUFA that is preferentially deposited in brain phospholipids and has been linked to dementia, Parkinson disease, Alzheimer disease (AD), cognitive function, mental stability, suicide, depression, bipolar

disorders, impulsivity, aggression, etc. (3–10). The content of DHA in the brain is 12–15%, 10- to 20-fold higher than any other (n-3) PUFA. A concern has been the lack of clinical trials investigating the impact of long-chain (n-3) PUFA on brain function. Recently, new clinical trials have reported that DHA appears to prevent loss of cognitive function in the elderly (4,11), supporting earlier results demonstrating DHA's protective effect on neural cells (12). The work of Walter Lukiw and Nicholas Bazan (13), of LSU's Neuroscience Center, report that oxidative products generated from DHA [i.e., neuroprotectin D1 (NPD1)] reduce amyloid β -peptide ($A\beta$) secretion by neuronal cells and protect these cells by increasing the expression of antiapoptotic genes. β -Amyloid peptides [i.e., β -amyloid precursor protein (β APP) and $A\beta$] and their destructive aggregates are central to the development and progression of AD. Dr. Lukiw (standing in for Dr. Bazan), discussed the role of DHA in brain cell survival and repair and its synaptic, neurotrophic, antiapoptotic, and antiinflammatory functions (14). He reviewed the current understanding of DHA and $A\beta$ metabolism. His presentation focused on the interactions of DHA and NPD1 on β APP processing and $A\beta$ peptide signaling and how they contribute to pathogenic and oxidative processes characteristic of aging and the AD process.

Arachidonic acid and the brain

One of the most important changes in this field is the link between arachidonic acid (AA) content and brain function. The level of AA in the brain is comparable to that of DHA. At 8–11% of the fatty acid phospholipids, it is severalfold higher than any other (n-6) PUFA (by comparison, linoleic acid content is ~1%). Recent studies have demonstrated that dietary AA appears to influence plasticity and preserve hippocampal mem-

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⁴ Abbreviations used: AA, arachidonic acid; $A\beta$, amyloid β -peptides; β APP, β -amyloid precursor protein; AD, Alzheimer disease; DHA, docosahexaenoic acid; NPD1, neuroprotectin D1.

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brane fluidity (15,16) and may provide some protection to oxidative stress via the activation of peroxisomal proliferator-activated receptor- γ (17). Furthermore, it has been shown that AA, as well as DHA, activates syntaxin-3, a critical factor in the growth and regeneration of neurons (18,19). Although AA is typically thought of in a negative context because it is the precursor to bioactive eicosanoids, it certainly has physiological importance in the brain. However, until recently, the impact of brain AA metabolism had yet to be directly linked to neurological disorders. The work by Dr. Stanley Rapoport, Brain Physiology and Metabolism Section Chief at the National Institute on Aging (NIH), investigates disturbed AA turnover in the brain and its relation to neurological diseases such as bipolar disorder. His presentation discussed how the brain requires preformed AA [there is little conversion of linoleic acid to AA in the brain (20)], its incorporation into phospholipid pools, release from these pools, and subsequent utilization (metabolism or oxidation) or reincorporation (reacylation) back into brain phospholipids (21). Of importance, this cycling cascade of AA in the brain appears to be very important in stabilizing repeated manic and depressive episodes, similar to those observed in bipolar disease. He discussed how modulating recycling of AA may be an important mechanism underlying the effective treatments for individuals with manic and depressive mood swings.

In summary, this symposium addressed the latest information regarding the potential impact of dietary PUFA and the health of the human brain, supported by the growing mechanistic studies delineating their function in brain metabolism. It has underscored the concept that both families of PUFA, the (n-6) and (n-3) families, are important in brain function, each possessing unique properties in maintaining neurological health.

Other articles in this symposium include references (14) and (21).

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