

# Alkyl-Acylglycerols and the Important Clinical Ramifications of Raising Plasmalogens in Dementia and Alzheimer's Disease

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## Abstract

A critical factor involved in the pathophysiology of Alzheimer's disease (AD) and related dementias is the decline of plasmalogens, a key glycerophospholipid required for normal neuron function. An accumulating body of evidence correlates low blood and brain plasmalogens with higher levels of AD pathology and lower cognition scores and indicates that declines in these phospholipids begin years before clinical symptoms develop. Furthermore, it has been recently reported that high blood plasmalogen levels neutralize the increased risk of dementia in persons who carry the APOE epsilon 4 allele, the most significant genetic risk factor for AD. There are over 30 common species of plasmalogens in the human body with different plasmalogen species playing different roles, depending on the organ and cell type. Accordingly, there is great interest in understanding how to selectively target plasmalogen augmentation for specific

health needs. For example, brain white matter is comprised of plasmalogens containing monounsaturated fatty acids, whereas gray matter is comprised of plasmalogens containing polyunsaturated fatty acids. Fortunately, the structure-activity and biochemistry of plasmalogen augmentation has been extensively studied in cell and animal models. Restoring and augmenting levels of selective plasmalogens can be achieved with dietary supplementation of 1-O-alkyl-2-acyl glycerol oils containing the desired fatty acid type at the 2-acyl position. Neuron-targeted 1-O-alkyl-2-acyl glycerol containing DHA has been shown to be neuroprotective and neuroactive in animal models of neurodegeneration. This review will discuss the mechanisms by which plasmalogen deficiency leads to Alzheimer's and/or dementia and the critical role that 1-O-alkyl-2-acyl glycerol oils can play in patients with those disorders.

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## Introduction

Dementia is a clinical syndrome involving progressive decline in two or more cognitive parameters, such as memory, language, executive and visuospatial function, personality, and behavior. Dementia leads to the inability to perform important functions and/or normal activities of daily living, as well as heartbreaking and frustrating interactions with family members. The most common form of dementia is Alzheimer's disease (AD), accounting for 60% to 80% of all dementia diagnoses globally.<sup>1</sup> Currently, more than 5 million people are living with AD.<sup>2</sup> By 2050, with the aging population in the United States, nearly 14 million people are expected to be living with the disease.<sup>2</sup> In the United States, Alzheimer's-related deaths have increased by 89% from 2000 to 2014.<sup>3</sup> AD is the sixth leading cause of death in the United States and the fifth leading cause of death in individuals 65 years and older.<sup>3</sup> Alzheimer's disease takes a significant toll on patients'

health and also represents a substantial economic burden with an estimated healthcare cost of \$305 billion.<sup>2</sup> By 2050, it is estimated that AD-associated expenditures could rise to \$1.1 trillion.<sup>2</sup>

AD is characterized by a number of pathologies including neurofibrillary tangles, amyloid plaques, neuroinflammation, ocular and microvascular pathologies, and significant cholinergic impairments.<sup>4</sup> A commonality associated with each of these is the decline in ethanolamine plasmalogens in the brain, eye, and vascular endothelium.<sup>4</sup> There is an extensive body of literature linking low blood and brain plasmalogens to dementia and AD. This review will explore the biochemical mechanisms of how low plasmalogen concentrations disrupt cognitive pathways in the brain and the neuroprotective effects of plasmalogen supplementation.

## The Role of Plasmalogens in the Brain

Plasmalogens are glycerophospholipids that play a critical role in brain health.<sup>5</sup> In the human body, plasmalogen ethanolamines (PlsEtn) are the primary form of these phospholipids with more than half of the ethanolamine phospholipids in the brain falling into this category.<sup>6</sup> Plasmalogen concentrations continue to rise until 30 to 40 years of age then experience a significant

decline by age 70.<sup>7</sup> In nondemented subjects, an increased prevalence of low plasmalogen levels have been found between 59 and 69 years of age.<sup>8</sup> As a form of lipids, plasmalogens are critically involved in structural and physiological aspects of brain health. After the adipose tissue, the brain boasts the next-highest lipid content, composing approximately half of the dry weight of the brain.<sup>9</sup> Phospholipids are the primary lipid in the brain while triglycerides predominate adipose deposits.<sup>9</sup> Phospholipids are essentially storage basins for long-chain polyunsaturated fatty acids such as docosahexaenoic acid (DHA), which are plentiful in brain tissue and are able to penetrate the blood-brain barrier (BBB) and enter neurons.<sup>9</sup>

### **The Involvement of Declining Plasmalogen Levels in Dementia and Alzheimer's**

An abundance of evidence indicates plasmalogen is deficient in the brain and blood in AD.<sup>8,10-13</sup> This decline in plasmalogen levels noted in dementia patients begins years before clinical symptoms develop.<sup>8</sup> In patients with AD, brain PlsEtn concentrations have been found to be reduced compared to age-matched controls,<sup>11,13,14</sup> and this decline in brain levels is associated with reduced serum concentrations.<sup>14</sup> Furthermore, serum PlsEtn concentrations correspond to cognition in patients with AD.<sup>15</sup> This evidence was gathered postmortem from subjects confirmed by autopsy to have AD, as well as from serum samples obtained at time of death in people with AD pathology.<sup>15</sup>

Additional data corroborates a relationship between serum concentrations of PlsEtn, especially PlsEtn that contains arachidonic acid or DHA, and the severity of cognitive impairment.<sup>8</sup> Han and colleagues confirmed the correlation between low plasmalogen levels and dementia.<sup>12</sup> They conducted a systematic investigation of plasmalogen concentrations in cellular membranes of gray and white matter from different brain regions of human volunteers with AD dementia. The study authors observed a significant decline in plasmalogen levels in the white matter of patients at a very early stage of AD. There was also a correlation between the deficiency in gray matter plasmalogen levels and the clinical dementia ratings of the AD patients. Patients with very mild dementia were 10 mol% deficient while participants with severe dementia were 30 mol% deficient. The results suggest the critical involvement of plasmalogen deficiency in the pathogenesis of AD and neurodegeneration. Inflammation-induced oxidative stress may worsen plasmalogen decline, which creates a vicious cycle by impairing the anti-inflammatory and antioxidant mechanisms of brain tissues.<sup>16</sup>

### **Low Plasmalogen Levels and Amyloid Beta**

The deposition of  $\beta$ -amyloid ( $A\beta$ ) plaques is a key characteristic of AD.<sup>17</sup>  $A\beta$  accumulation is also detected in nondemented humans as young as 40 years old, and its

prevalence increases with age.<sup>8</sup> One mechanism by which plasmalogens may protect against AD is through their inhibitory effect on  $A\beta$  plaque formation. Goodenowe and associates found a correlation between reduced serum PlsEtn and the presence of  $A\beta$  plaques in the central nervous system (CNS).<sup>8</sup> Furthermore, the decline of serum PlsEtn occurs at the same time that  $A\beta$  accumulation begins in humans.<sup>8</sup>

Rothhaar and associates demonstrated that reduced plasmalogen levels are not just a consequence of AD, but are also involved in the deposition of  $A\beta$  plaques, which may contribute to AD pathology.<sup>18</sup> The study authors observed in human AD postmortem brains that plasmalogens were associated with a decline in the activity of  $\gamma$ -secretase, an enzyme that catalyzes the synthesis of  $A\beta$  by influencing amyloid precursor protein (APP) processing. The researchers concluded that  $A\beta$  reduces plasmalogen concentrations, which in turn directly increases  $\gamma$ -secretase activity, resulting in an even greater synthesis of  $A\beta$  plaques.

Additional support for the role of plasmalogens in  $A\beta$  is the involvement of these phospholipids in cholesterol homeostasis.<sup>8</sup> Increased membrane cholesterol concentrations lead to accumulation of  $A\beta$  peptides by a mechanism that involves APP processing.<sup>8</sup> The vast majority of APP is processed through the  $\alpha$ -secretase pathway, which is not associated with AD.<sup>8</sup> However, some is diverted to the  $\beta$ -secretase pathway, a pathological process that leads to  $A\beta$  deposition.<sup>8</sup> A phospholipid-rich membrane domain is a storehouse for the non-pathological  $\alpha$ -secretase whereas  $\beta$ -secretase is found in cholesterol-rich domains,<sup>8</sup> lending further support to the idea that phospholipids are protective against  $A\beta$  accumulation. Furthermore, increases in membrane cholesterol lead to a reduction in  $\alpha$ -secretase activity and an increase in  $\beta$ -secretase leading to  $A\beta$  accumulation.<sup>19,20</sup> Other evidence that cholesterol is linked to  $A\beta$  accumulation is that a high-cholesterol diet is known to elevate  $A\beta$  deposition.<sup>21</sup>

Postmortem membrane lipid analyses of AD patients have revealed that there is a positive correlation between dementia severity and membrane cholesterol<sup>22</sup> and a negative association with membrane plasmalogens.<sup>12</sup> Furthermore, oxidative stress conditions that cause a decline in membrane plasmalogen content also elevate membrane cholesterol.<sup>8,23</sup> This points to a strong link between PlsEtn and cholesterol concentrations.

### **The Relationship Between APOE and Plasmalogens**

Apolipoprotein E (APOE) is the primary lipoprotein in the brain,<sup>24</sup> with the presence of the APOE epsilon 4 allele posing the most significant genetic risk factor for AD.<sup>25</sup> Research indicates that the effects of APOE on AD and dementia may be mediated by low PlsEtn. Goodenowe and Senanayake investigated the correlations and possible interplay between the APOE genotype and serum PlsEtn

on cognition and dementia in 1,205 elderly individuals.<sup>26</sup> They found that the net effect of the APOE genotype on cognition and the prevalence of dementia was dependent upon plasmalogen concentrations of the subjects. Regardless of the APOE genotype, the probability of dementia neared zero when the PlsEtn Biosynthesis Value (PBV, a combination of three important PlsEtn species) was higher. Older age was associated with a greater probability of dementia, but a higher PBV index was associated with a near-zero probability of dementia, regardless of age. This indicates that higher PlsEtn concentrations are protective against dementia even in the presence of other risk factors. Both APOE and PlsEtn affect cholesterol homeostasis, which is a likely mechanism by which each of these factors influence the pathogenesis of AD.<sup>26</sup>

### **Other Mechanisms of Plasmalogen Deficiency in Alzheimer's and Dementia**

Other mechanisms of action may explain the deleterious effects of plasmalogen deficiency on cognitive function. The decreased cognitive function in dementia is due to a decline in postsynaptic cholinergic function.<sup>27,28</sup> PlsEtn deficiency has a detrimental effect on choline uptake as neurons may depend upon it during states of low choline status.<sup>27,28</sup> During depletion of free choline in the cholinergic nerve terminal, membrane phospholipids such as PlsEtn are degraded to replenish choline stores.<sup>27,28</sup> Impaired lipid processing in the brain is also associated with metabolic disorders such as diabetes.<sup>9</sup> AD has been called type 3 diabetes and several epidemiological studies have found a correlation between diabetes mellitus and dementia.<sup>29</sup> Insulin resistance can result in a decline in brain insulin and impaired regulation of an insulin-degrading enzyme, which also breaks down A $\beta$ .<sup>29</sup> This leads to A $\beta$  accumulation and brain insulin resistance.<sup>29</sup> Plasmalogen levels are negatively correlated with insulin resistance in obese human subjects.<sup>30</sup>

### **The Dramatic Effects of Selective Plasmalogen Augmentation**

Science has shown that selectively elevating specific plasmalogens can lead to beneficial effects with implications for dementia and AD. For example, Wood and colleagues investigated the structure-activity of 1-O-alkyl-2-acyl glycerols on the *in vitro* formation of A $\beta$ 1-42, the protein found in amyloid plaques, and observed that 1-O-alkyl-2-acyl glycerols with DHA at the 2-acyl position not only blocked the A $\beta$ 1-42 elevating effect of cholesterol but also dose dependently lowered concentrations of A $\beta$ 1-42 by enhancing the activity of non-amyloidogenic  $\alpha$ -secretase pathway.<sup>4</sup> Three other plasmalogen precursors (stearic, oleic, and linoleic) that exhibited other side chains had no effect. In a related study, Mankidy and colleagues investigated the structure-activity of 1-O-alkyl-2-acyl glycerols on cholesterol

regulation and demonstrated that 1-O-alkyl-2-acyl glycerols containing DHA at the 2-acyl position dose dependently lowered cellular cholesterol levels by increasing cholesterol clearance and that this mechanism was more effective at lowering cholesterol than statin-induced HMG-CoA inhibition.<sup>31</sup>

1-O-alkyl-2-acyl glycerols have been extensively studied in preclinical animal studies. 1-O-alkyl-2-acyl glycerols are orally bioavailable with a 10 mg/kg dose resulting in a 2-fold elevation and a 50 mg/kg dose in an almost 4-fold increase in blood DHA-plasmalogen levels. Elevated levels were also seen in the kidney and neocortex. 1-O-alkyl-2-acyl glycerols have been shown to prevent neurodegeneration in a mouse model of Parkinson's disease, and may contribute to remyelination.<sup>4,32</sup> It is noteworthy that reduced myelination is involved in AD pathology, and myelin markers such as plasmalogens are reduced in AD.<sup>12</sup>

Organelles known as peroxisomes are the sole site of DHA and plasmalogen biosynthesis.<sup>33</sup> However, peroxisomal function weakens with age.<sup>34,35</sup> This substandard peroxisomal function results in a decline in the production of PlsEtn and DHA.<sup>36,37</sup> 1-O-alkyl-2-acyl glycerol oils bypass peroxisomal biosynthetic pathways for both plasmalogens and DHA that are impaired in aging and disease.<sup>4</sup> This serves to restore or enhance DHA and plasmalogen levels, thereby improving synaptic and membrane functions negatively impacted by AD and that are associated with clinical and pathological manifestations of the disease.<sup>4</sup> DHA dramatically declines with age, and with increasing severity of AD, DHA-PlsEtn levels fall in studies using post-mortem brain samples and pre-mortem serum samples.<sup>4</sup> Data indicates DHA-PlsEtn levels drop according to the severity of dementia,<sup>12</sup> and subjects with low, moderate, and severe dementia have progressively lower concentrations of DHA-PlsEtn.<sup>4</sup> Phospholipid-linked DHA, which contains plentiful levels of plasmalogens, significantly benefits cognition, whereas triglyceride-linked DHA has only a small effect.<sup>38</sup>

Based upon extensive peer-reviewed publications, 1-O-alkyl-2-acyl glycerol oils appear to be a highly effective natural approach to resolving plasmalogen deficits and elevating plasmalogens to protective levels. 1-O-alkyl-2-acyl glycerol oils work with the body's natural biochemical pathways in the liver and gut, which markedly raises blood plasmalogen levels.<sup>39</sup> In the gut, they release a plasmalogen precursor. This plasmalogen precursor retains its DHA sn-2 fatty acid, which allows it to be absorbed into the circulation, where it is converted to the target plasmalogen.<sup>39</sup> Alkylglycerols have a well-documented safety profile and have been administered to humans at large doses for long periods of time. For example, Das et al treated genetically compromised infants for up to 4 years with alkylglycerols with no adverse effects.<sup>40</sup> Recently, 1-O-alkyl-2-acyl glycerol oils with either DHA (ProdromeNeuro) or oleic acid (ProdromeGlia)

at the 2-acyl position have become commercially available. In addition, the company offering these 1-O-alkyl-2-acyl glycerols also offers extensive blood plasmalogen testing services (ProdromeScan).

In contrast, orally ingested phospholipids are degraded by gut enzymes known as phospholipases which remove the 2-acyl fatty acid in these phospholipids in order to produce a lyso-phospholipid, which is then absorbed.<sup>39</sup> This eliminates the ability to target specific phospholipid species, like those containing 2-acyl DHA.<sup>39</sup> In addition, the vinyl ether bond of intact plasmalogen phospholipids is not stable under acidic conditions. When exposed to acids, the vinyl ether bond is oxidized into aldehydes. Recently published research data showed that 60% of PlsEtn is degraded at pH = 2 and 100% is degraded at pH = 1.<sup>41</sup> Considering that the average acidity of the human stomach ranges from pH 1.5 to 3.5, a high proportion of ingested plasmalogen phospholipids will be converted to aldehydes in the stomach. Currently there are no published studies that have investigated the relationship between stomach acid conditions, plasmalogen phospholipid digestion and aldehyde formation, absorption and toxicity.

Considering the potential toxicities of aldehydes,<sup>42</sup> the oral administration of large doses of intact plasmalogen phospholipids either in pure form or from animal extracts should be approached with caution until further research is performed in this area. Therefore, 1-O-alkyl-2-acyl glycerol-based plasmalogen supplements are the more clinically prudent approach to elevating plasmalogens based upon the scientific literature.

## Conclusion

Low plasmalogen levels occur with age and are strongly associated with Alzheimer's disease and dementia. This decline in plasmalogen concentrations observed in dementia patients begins years before the onset of clinical symptoms. Plasmalogen deficiency also contributes to the deposition of A $\beta$  plaques and is associated with APOE, a genetic risk factor for AD. In the human body, PlsEtn is the primary form of these plasmalogen phospholipids. Restoring plasmalogen levels can eliminate the deficiency that occurs with age and provide pronounced benefits in AD and dementia. 1-O-alkyl-2-acyl glycerol oils are used to replenish plasmalogen levels using either DHA- or oleic acid-plasmalogen precursors, which offers significant advantages over other approaches. 1-O-alkyl-2-acyl glycerol oils bypass both DHA and plasmalogen synthesizing pathways that are weakened with age, elevating levels of these crucial brain health substances. The evidence clearly points to the elevation of selective plasmalogens as having strong clinical ramifications in the treatment of AD and dementia.

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