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Review

Diacylglycerols as biomarkers of sustained immune activation in Proteinopathies associated with dementia

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ABSTRACT

Cognitive decline is a devastating clinical condition, heavily correlated with age progression. In the cases of Alzheimer's disease, Parkinson's disease, and Lewy body disease, the common neuropathologies are proteinopathies and neuroinflammation. Herein, we review current lipidomics findings and conclude that brain and circulating diacylglycerols represent biomarkers of this ongoing sustained immune response, presumably involving microglia. We further hypothesize that a logical next step will be to evaluate biomarkers of immune activation in a cohort of patients with Mild Cognitive Impairment (MCI) and subsequently attempt to provide therapeutic intervention with anti-inflammatory therapy in MCI patients with immune activation. Although this is an urgent and theoretically safe therapeutic trial, it will likely necessitate government support.

1. Introduction

With the aging of the “baby-boomer” generation, there is an ever-increasing expansion of the geriatric population, placing a tremendous burden on caregivers and the healthcare system [1]. The age-associated proteinopathies, including mixed pathologies, are serious neurological disorders that ultimately result in cognitive deficits in many geriatric patients who ultimately becoming institutionalized.

Omics technologies have been applied extensively in attempts to understand the biochemistry of the neuropathological events that ultimately result in cognitive dysfunction.

2. Diacylglycerol (DAG) findings

One of these omics technologies is lipidomics, which has been utilized to examine alterations in the lipidome both in the brain and in the blood of patients with proteinopathies. While a number of changes have been found in glycerophospholipids and sphingolipids (reviewed in references [2] and [3]), a unique and consistent observation, by multiple laboratories, is that diacylglycerol (DAG) levels are augmented in the neocortex in Alzheimer's disease (AD) [4–6], subcortical ischemic vascular dementia ± AD [7], mild cognitive impairment (MCI) [5–6], Parkinson's disease (PD), [8–9] and Lewy body disease (LBD) [8]. In addition, increased circulating levels of DAGs have been detected in plasma and serum studies of MCI [10] and AD [10–12] patients (Fig. 1). In the most recent study [13], elevated cortical DAG levels were again detected in early and late AD, despite the small sample size utilized for analyses.

Two very important observations of these studies include:

1. While DAG levels were increased in a postmortem evaluation of the frontal cortex of subjects with MCI and AD, there were no increases in DAG levels in the “late age” (> 85 yr) control group (Fig. 1). These were individuals who had no cognitive deficit at death but on autopsy demonstrated significant AD neuropathology and have been termed Non-Demented individuals with significant Alzheimer's Neuropathology (NDAN) [10,13–18]. Similarly, the most recent analysis of cortical DAGs, these levels were not elevated in the NDAN group [13]. These data do not support a role of amyloid deposition or neuritic plaques in the induction of DAG accumulation.
2. In our study of a large sample set of MCI and AD plasma samples (Fig. 1), we found that not all MCI or AD patients had elevated serum levels of DAGs [10]. Augmented plasma DAG levels were monitored in a subset of patients encompassing 25 to 30% of MCI subjects and 40 to 45% of AD subjects. These data support the concept that patients diagnosed with AD, via clinical criteria, represent a heterogeneous population with more than one biochemical/neuropathological path to cognitive dysfunction and often with mixed neuropathologies [19–22].

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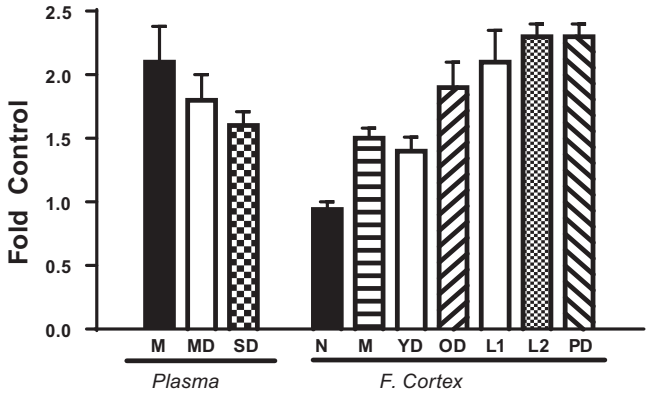

Fig. 1. DAG levels as fold control in the plasma and frontal (F) cortex in subjects with proteinopathies. M, MCI; MD, mild dementia; SD, severe dementia; N, NDAN (> 85 yr); YD, young dementia (< 85 yr); OD, old dementia (> 85 yr); L1, Lewy body disease; L2, Lewy body disease with cortical AD pathology; PD, Parkinson's disease. DAG levels were significantly increased ($p < 0.05$) in all groups relative to age-matched controls except for the old controls (NDAN) that were unaltered. Data from [5–6,9–11]. EDTA plasma samples were obtained via standard practice and stored at −80 °C prior to analysis [10–11] while frontal cortex was dissected from postmortem tissue and flash frozen prior to storage at −80 °C [5–6,9].

3. Relevance of DAG Findings

DAG pools are tightly regulated as a result of the critical structural and signal transduction roles of these neutral lipids. With regard to structural roles, DAGs are precursors of glycerophospholipids [5–6], are required in the Golgi for transport carrier biogenesis [23], and are important lipids in the endoplasmic reticulum and nuclear envelope [24–25]. With regard to signal transduction, DAGs directly modulate nuclear signal transduction [26–27] and are precursors of endocannabinoid signal transduction [28]. DAGs also can modulate signal transduction via activation of protein kinases involved in synaptic transmission. These include PKC, PKD, Ca(2 +)/calmodulin-dependent protein kinase (PKCaMII), RasGRP1/Ras/Erk MAPK [26,29–30]. Immune function is also modulated by DAGs which are involved in immunological synapse function [31] and respiratory burst in microglia [32].

Given these diverse roles and functions of DAGs, slight alterations in otherwise tightly regulated systems can yield dramatic effects on normal cell processes. Additionally, the critical roles of DAGs in synaptic function may well be a critical component in the eventual cognitive dysfunction that develops in proteinopathies.

4. Mechanisms involved in DAG accumulation in proteinopathies

There are a diverse number of metabolic changes that could lead to DAG accumulation in proteinopathies (Fig. 2). The major pathway for regulating DAG levels involves metabolism by DAG kinase (Fig. 2), an enzyme that is important in synaptic function and is down-regulated in AD [32–34]. Based upon other research in this area, it is possible that increased expression of phospholipase C (PLC) [35–37] and phospholipase D (PLD) [38–39] results in the accumulation of DAGs via metabolism of glycerophospholipids. In this regard, AD neocortex phosphatidylethanolamines are decreased suggesting that PLC and PLD metabolism of this glycerophospholipid pool may be a source of augmented DAGs in AD [5–6]. Gene variants of PLD [40–43] and PLC [44] in AD may be involved in these lipid changes.

Another potential source of DAGs is from sphingomyelin synthesis (Fig. 2). This involves the transfer of the phosphocholine headgroup from phosphatidylcholines to ceramides via sphingomyelin synthase. While sphingomyelins and phosphatidylcholines are not dramatically altered in AD [5–6], sphingomyelins are increased in the neocortex of LBD subjects with AD pathology and phosphatidylcholines are decreased in the neocortex of Parkinson's subjects, LBD subjects and LBD subjects with AD pathology [9]. These data suggest that PLC, PLD, and sphingomyelin synthase may be involved in DAG generation in PD and LBD.

The next question is what conditions result in activation of PLC and PLD. A clear answer to this may be indicated by the number of publications demonstrating that immune activation results in the upregulation of PLC [45–46] and PLD [47–50]. Additionally, in our research we have monitored increased serum levels of DAGs and sphingomyelins in experimental models of immune activation [51]. Based on these findings we speculate that the monitored elevations of DAG levels in all proteinopathies represent a potential biomarker of immune activation. Since we monitor these alterations in DAGs in MCI (5–6), our data would further suggest that there is immune activation early in the biochemical cascade of proteinopathies and that this is sustained throughout disease development. Resolving or blunting this process may have significant clinical benefit if therapeutic intervention is early enough.

5. Immune activation in proteinopathies

Microglial activation is associated with all proteinopathies [52–59]. In vivo imaging has also demonstrated that immune activation occurs early in the disease process, as demonstrated by microglial activation in MCI patients [59–61]. This immune activation can be quantitated by monitoring cytokines and other immune biomarkers in postmortem brain [62] and in the plasma [63–65] of subjects with proteinopathies.

A potential role of inflammation in the augmentation of plasma DAGs in MCI and AD, and neuroinflammation in the augmentation of brain levels of DAGs may be important since inflammation is known to result in the induction of PLC [45–46] and PLD [47–50]. In dementias, brain microglia presumably are involved in the induction of PLC, PLD,

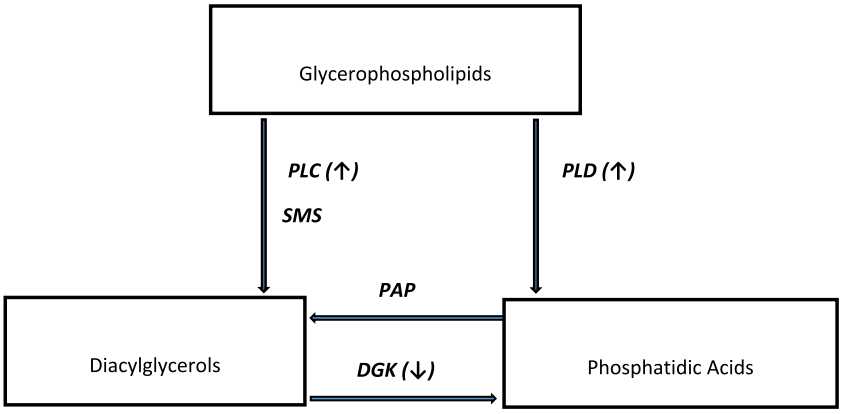

Fig. 2. Schematic of DAG synthesis and metabolism. DGK, diacylglycerol kinase; PAP, phosphatidic acid phosphatase; PLC, phospholipase C; PLD, phospholipase D; SMS, sphingomyelin synthase. ↑ Arrows represent increased enzyme expression in Alzheimer's disease and in animal models and human conditions of immune activation. Decreased (↓) enzyme expression of DGK is present in Alzheimer's disease.