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Mini-review

The essential role of lipids in Alzheimer's disease

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ABSTRACT

In the absence of efficient diagnostic and therapeutic tools, Alzheimer's disease (AD) is a major public health concern due to longer life expectancy in the Western countries. Although the precise cause of AD is still unknown, soluble β-amyloid (Aβ) oligomers are considered the proximate effectors of the synaptic injury and neuronal death occurring in the early stages of AD. Aβ oligomers may directly interact with the synaptic membrane, leading to impairment of synaptic functions and subsequent signalling pathways triggering neurodegeneration. Therefore, membrane structure and lipid status should be considered determinant factors in Aβ-oligomer-induced synaptic and cell injuries, and therefore AD progression. Numerous epidemiological studies have highlighted close relationships between AD incidence and dietary patterns. Among the nutritional factors involved, lipids significantly influence AD pathogenesis. It is likely that maintenance of adequate membrane lipid content could prevent the production of Aβ peptide as well as its deleterious effects upon its interaction with synaptic membrane, thereby protecting neurons from Aβ-induced neurodegeneration. As major constituents of neuronal lipids, *n*-3 polyunsaturated fatty acids are of particular interest in the prevention of AD valuable diet ingredients whose neuroprotective properties could be essential for designing preventive nutrition-based strategies. In this review, we discuss the functional relevance of neuronal membrane features with respect to susceptibility to Aβ oligomers and AD pathogenesis, as well as the prospective capacities of lipids to prevent or to delay the disease.

1. Introduction

Alzheimer's disease (AD) is a progressive dementia that manifests in early stages as a profound inability to form new memories. Age is the major risk factor for the non-familial form of AD (up to 99% of cases), which at least partly explains the dramatic increase in AD prevalence in countries where life expectancy is growing [1]. Many questions about pathogenesis of this devastating disease still remain unanswered and satisfying therapeutic options are few [2]. Given the heavy individual and societal burdens inflicted by AD, there is enormous medical need for the development of novel therapeutic strategies that target or even better prevent from the mechanisms leading to dementia. In this context, it becomes essential to identify the molecular actors and pathways involved in AD pathogenesis.

Due to the progressive and – yet – irreversible nature of AD, very early stages (preclinical and mild cognitive impairment) may be due to synaptic dysfunction caused by Aβ peptide under soluble oligomeric form, long before widespread synaptic loss and neurodegeneration. Indeed, clinical studies have shown that soluble Aβ levels rather than amyloid deposits are better correlated with dementia severity [3]. Furthermore, in the brain of AD patients, Aβ oligomeric forms mainly target synapses affected early in the pathogenesis [4]. Cognitive deficits appear before amyloid deposition in AD transgenic mice models [5], which strongly implicate

Abbreviations: Aβ, amyloid-β peptide; AD, Alzheimer's disease; ApoE, apolipoprotein E; APP, amyloid precursor protein; ARA, arachidonic acid; $cPLA_2$, cytosolic phospholipase A_2; COX, cyclooxygenase; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; LOX, lipoxygenase; LTP, long-term potentiation; PS1, presenilin-1; PUFA, polyunsaturated fatty acid; S1P, sphingosine-1-phosphate; SMase, sphingomyelinase.

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soluble forms of Aβ whose intracerebral injection inhibits long-term potentiation (LTP), a paradigm for memory [6], as well as cognitive functions [7].

Fusogenic properties of soluble Aβ suggest that interaction with plasma membrane occurs among the initial events leading to impairment of synaptic functions and subsequent neurodegeneration [8]. It is thus essential to identify the biological factors that could modulate these early interactions and their noxious consequences. Besides age and gender, education level and social activities, dietary parameters represent common risk factors for neurodegenerative and cardiovascular diseases, leading to the idea that nutrition could offer powerful tools for delaying onset of AD or slowing its progression. Among them, lipid status has been identified as a key parameter in AD pathogenesis by numerous epidemiological, clinical, animal or cellular studies [9]. This is especially the case for docosahexaenoic acid (DHA; *n*-3, C22:6), a fatty acid essential for cerebral functions and whose decline has been reported in the brain and plasma of AD patients [10].

2. Lipids influence neuronal susceptibility to amyloid stress

2.1. Membrane architecture is determinant for Aβ neurotoxicity and production

A growing body of evidences supports the notion that membrane destabilization by Aβ oligomers may represent the primary mechanism of pathogenesis. Indeed, exposure to soluble Aβ causes a rapid and reversible leakage of calcium that can be inhibited by anti-oligomer antibody. Such an increased lipid bilayer conductance without forming discrete pores suggests that Aβ oligomers could directly induce a profound remodelling of plasma membrane. In that way, we have shown that exogenous cholesterol and DHA protect cortical neurons in primary cultures from Aβ-induced apoptosis, while cholesterol depletion increases Aβ-oligomers neurotoxicity [11,12]. Since steric incompatibility of the rigid steroid moiety for highly disordered DHA chain promotes lateral segregation of lipids into rafts [13,14], it can be deduced that membrane lipid status is strongly involved in neuron susceptibility to Aβ oligomers and therefore represents a goal for prevention. Accordingly, it is well known that inheritance of apolipoprotein ε4 allele (ApoE4) is a major risk factor for sporadic AD [15]. ApoE proteins belong to the family of plasma lipid-binding proteins involved in triglycerides and cholesterol transport and delivery, but it is also worthy to note that ApoE proteins also contribute to the clearance of Aβ peptide through binding to lipoprotein receptors [16].

Although the link between ApoE4, cholesterol and AD is still not clear, it becomes obvious that cholesterol can modulate AD pathogenesis by influencing Aβ production and neurotoxicity [9]. Aβ peptides are derived from proteolytic cleavage of the membrane-bound amyloid protein precursor (APP). APP is metabolised by two possible pathways: the non-amyloidogenic pathway involves a sequential cleavage of APP by α- and β-secretases, leading to the release of a secreted neurotrophic APP ectodomain called sAPPα, while the amyloidogenic pathway results in Aβ release as well as loss-of-function of truncated sAPPα [17]. As the α- and β-secretases compete for the same substrate, distribution of APP between the two alternative pathways is thus tightly regulated. Numerous studies support the hypothesis that dynamic partitioning of APP and its proteolytic enzymes in different membrane domains could be the main regulatory mechanism involved (Fig. 1). Accordingly, it was found that β- and γ-secretase activities are concentrated and optimized in lipid rafts, while α-secretase and APP are mainly found in non-raft regions [18]. Consistent with that, depletion in cholesterol which is highly enriched in rafts has been demonstrated to decrease Aβ production [19], leading to the exciting perspectives of statin-based treatment as a mean to lower cholesterol levels. Statins have been reported to reduce AD risk [20,21] and to prevent Aβ-induced neuronal loss and memory impairment [22], but contradictory data have also been published [23]. This suggests that the appropriateness of statin therapy is not established at this time [24,25] and the fact that a moderate decrease in cholesterol levels results in increased Aβ production in primary hippocampal neurons [26] indicates that the link between cholesterol and AD requires to be more clearly elucidated.

In this context, DHA has been recently demonstrated to promote the non-amyloidogenic pathway, resulting in reduced Aβ levels in AD cellular models [27]. Though dietary DHA clearly leads to

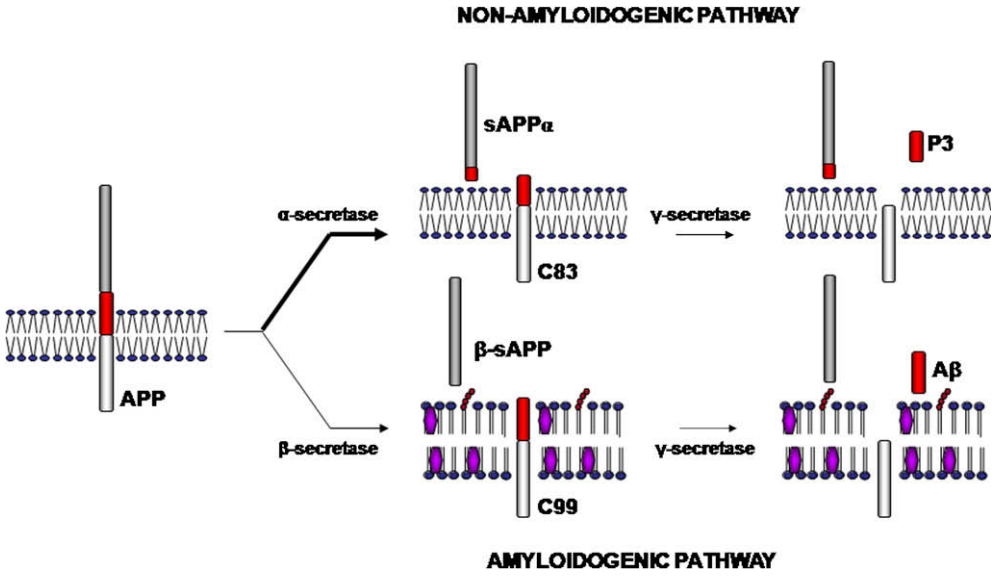

Fig. 1. Alternative processing of APP. APP is mainly metabolised through the non-amyloidogenic pathway involving a sequential cleavage by α- and β-secretases, leading to release a secreted neurotrophic protein called sAPPα. On the other hand, the amyloidogenic pathway requires β- and γ-secretase activities and leads to Aβ production. This pathway mainly occurs in rafts represented here by membrane domains enriched in cholesterol (purple hexagons) and gangliosides (with red tails).