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Review article

Resolution of inflammation, n − 3 fatty acid supplementation and Alzheimer disease: A narrative review

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ABSTRACT

In patients with Alzheimer's disease (AD), a persistent and unresolved neuroinflammatory process can contribute to neuronal loss and a decline in their cognitive and functional abilities. Recent studies have demonstrated that the ability to resolve inflammation is impaired in the brains of patients with AD. Preclinical evidence demonstrates the potential of therapeutic interventions on the resolution phase of inflammation in AD. Supplementation of omega-3 fatty acids (n − 3 FAs), precursors for specialized pro-resolving mediators, emerged as a possibility for prevention and management of AD. Here, we provide a narrative review of resolving inflammation in AD and the role of n − 3 FA supplementation in AD.

1. Introduction

Resolution is the process of restoring affected tissue at the end of an inflammatory response. If this process does not occur, it may lead to chronic inflammation, which plays an important role in the pathophysiology of many diseases.

In the last decade, understanding that the resolution of inflammation is an active and controlled process, orchestrated by specific mediators and cell subtypes (Alessandri et al., 2013; Serhan, 2014), inaugurated a new era for understanding diseases stemming from chronic inflammation. A suitable inflammatory response is essential to maintain a healthy system. However, it must be self-limited by ensuring complete tissue restoration after depletion of the injury has occurred. Thus, adequate engagement of resolution pathways is necessary, which is characterized by sequential events: clearing the injury stimulus; switching from release of pro-inflammatory to pro-resolving mediators; terminating the recruitment of polymorphonuclear cells (PMNs) followed by their apoptosis in conjunction with the influx of monocytes, which differentiate into macrophages; and initiating efferocytosis of PMNs by macrophages, which egress to the blood or lymphatic circulation (Alessandri et al., 2013; Buckley et al., 2014; Buckley et al., 2013).

Pro-resolving molecules comprise gases, proteins and lipids (Buckley et al., 2013). Lipids are the most studied and can be called specialized pro-resolving lipid mediators (SPMs). They are formed by the oxidation of arachidonic acid (AA; C20:3ω − 6), ω − 3 eicosapentaenoic acid (EPA; C20:5ω − 3), and docosahexaenoic acid (DHA; C22:6ω − 3). Lipoxins, the first class ever described (Serhan et al., 1984), are derived from AA, while the E series resolvins originate from EPA and D series resolvins, maresins and protectins are generated from DHA (Buckley et al., 2014; Buckley et al., 2013). The human enzymes involved in the production of lipid SPMs include the epithelial cell-, eosinophil-, or monocyte-derived 15-lipoxygenase (15-LOX), leukocyte-derived 5-LOX, platelet-derived 12-LOX, and cyclooxygenase 2 (COX2) (Buckley et al., 2013; Serhan, 2014). These enzymes are present in several tissues and generate, in the acetylated form, precursors of aspirin-triggered lipoxins (Claria and Serhan, 1995), resolvins (Serhan et al., 2000; Serhan et al., 2002), and protectins (Serhan et al., 2011). The known receptors for pro-resolving molecules are often redundant (Im, 2012) and include the formyl peptide receptor type 2 or lipoxin A4 receptor (FPR2/ALX) for lipoxin A4 (LXA4), annexin A1 (ANXA1), and resolvin (Rv) D1 (Chiang et al., 2006; Cooray et al., 2013); a G protein-coupled receptor 32 (GPR32) for lipoxin A4 and RvD1 (Krishnamoorthy et al., 2010); a chemokine-like receptor 1 (ChemR23) for RvE1 (Arita et al., 2005; Arita et al., 2007; Herova et al., 2015); and a leukotriene B4 receptor (LTB_4R or BLT1) for RvE1 (Arita et al., 2007).

Alzheimer's disease (AD) is a neurodegenerative disorder pathologically characterized by the deposition of senile plaques composed of a 39–42 amino acid molecule called beta-amyloid peptide (Aβ) (Campion et al., 2016; Hardy and Higgins, 1992) and the presence of intracellular neurofibrillary tangles. These tangles are formed by the aggregation of a hyperphosphorylated microtubule-associated protein called tau

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protein (p-tau). The presence of these tangles is related to the severity of dementia (Arriagada et al., 1992; Campion et al., 2016). A synergic interaction between the amyloid and tau pathology possibly occurs in AD. Neurotoxic Aβ species modulate kinases and phosphatases inducing tau misfolding. Tau aggregation mediates synaptic dysfunction and neuronal death, which are the molecular signatures of cognitive decline in AD (Bloom, 2014; Khan and Bloom, 2016). Additionally, persistent and unresolved neuroinflammation also exists in AD, which is characterized by activation of microglia and astrocytes, recruitment of peripheral immune cells and excessive production of pro-inflammatory mediators (Elali and Rivest, 2015; Heneka et al., 2015; Osborn et al., 2016). In AD, chronic inflammation may contribute to disease progression and neuronal loss (Glass et al., 2010; Heneka et al., 2015). Therefore, new possibilities to comprehend and develop therapies targeting AD pathogenesis have been discussed. In this narrative review, we provide an update on the resolution of inflammation in AD and also the role of omega-3 fatty acid (n − 3 FA) supplementation in patients with AD.

2. Methods

We used a few key terms to search for studies on PubMed, Web of Science, SCOPUS and Cochrane databases (Fig. 1). Original research articles written in English were included, as well as systematic reviews and meta-analyses that addressed the resolution of inflammation in AD and the role of polyunsaturated fatty acids supplementation in AD patients. Articles that did not focus on this issue, as well as general review papers were excluded. First, we screened the database results based on titles and abstracts of the articles. Next, all articles were read completely before being selected. Other articles were included after this preliminary selection. The selection process is described in Fig. 1.

3. Results

A total of 50 publications that addressed the resolution of inflammation and the role of n − 3 FAs supplementation in AD were selected (Fig. 1). The main conclusions obtained from these publications are described in the subsections below.

3.1. Dysregulation of pro-resolving mediators in Alzheimer's disease

Increasing evidence indicates the existence of an important imbalance between several pro-resolving molecules in AD. It is possible that some disturbance in these mediators may be part of the aging process and occurs prominently during AD pathology (Table 1).

Urinary levels of LXA4 decrease progressively with healthy aging (Gangemi et al., 2005), indicating that an impairment in the production of SPMs may occur in the immunosenescent phenotype even with pro-inflammatory upregulation. Levels of maresin 1 (MaR1), neuroprotectin D1 (NPD1), and RvD5 are reduced in the entorhinal cortex of patients with AD. This is a brain area in the vicinity of the hippocampus, which is affected early on in the disease (Zhu et al., 2016). The down-regulation of NPD1 in AD brains is important, with 20-fold lower levels in the Cornu Ammonis region 1 (CA1) of the hippocampus in subjects with AD when compared to age-matched controls (Lukiw et al., 2005).

Levels of LXA4 were lower in the cerebrospinal fluid (CSF) of AD patients when compared to those with mild cognitive impairment (MCI) and subjective cognitive impairment (SCI). Moreover, levels of LXA4 and MaR1 were lower in the hippocampus of AD patients than in that of controls without dementia. Additionally, a high correlation between CSF levels of LXA4 and RvD1 has been demonstrated, as well as a positive correlation between these SPMs and performance on the Mini-Mental State Examination (MMSE) in AD, SCI and MCI patients (Wang et al., 2015c).

By contrast, proteic pro-resolving mediator ANXA1 was found up-regulated in the brain of AD patients comparing to age-matched controls. This finding could be related to higher ANXA1 expression in activated microglia, present mainly in brain gray matter and macrophages associated to amyloid plaques (McArthur et al., 2010).

3.2. Pro-resolving receptors in Alzheimer's disease

Many pro-resolving receptors are redundant as they bind to more than one ligand. GPR32 is present in SH-SY5Y neuroblastoma and this receptor plus FPR2/ALX are present CHME3 microglial cells (Zhu et al., 2016). The FPR2/ALX and ChemR23 are also detected in astrocytes (Wang et al., 2015c) and microglia (Rey et al., 2016). An immunohistochemical study demonstrated, in some areas of the hippocampus, a stronger labeling for FPR2/ALX and ChemR23 was observed in glial and pyramidal neurons of AD subjects as compared to that in controls. The upregulation of the ChemR23 was also demonstrated in the brains of subjects with AD by Western blot (Wang et al., 2015c). Additionally, FPR2/ALX and ChemR23 were upregulated after an inflammatory challenge, wherein an increase in FPR2/ALX expression was observed at 6 h and 18 h, and a decrease was observed at 24 h, post-LPS; a peak in ChemR23 expression was verified at 24 h post-LPS (Rey et al., 2016).

3.3. Enzymes of SPM synthesis in AD

Some studies have investigated enzymatic pathways in an attempt to explain the dysregulation of SPMs in AD. Microglia express 5-LOX and 15-LOX when challenged by LPS (Rey et al., 2016). The 15-LOX-2, which converts AA exclusively to 15*S*–hydroperoxyeicosatetraenoic acid (15-HPETE), is present in both microglia and astrocytes and is overexpressed in the hippocampus of patients with AD (Wang et al.,

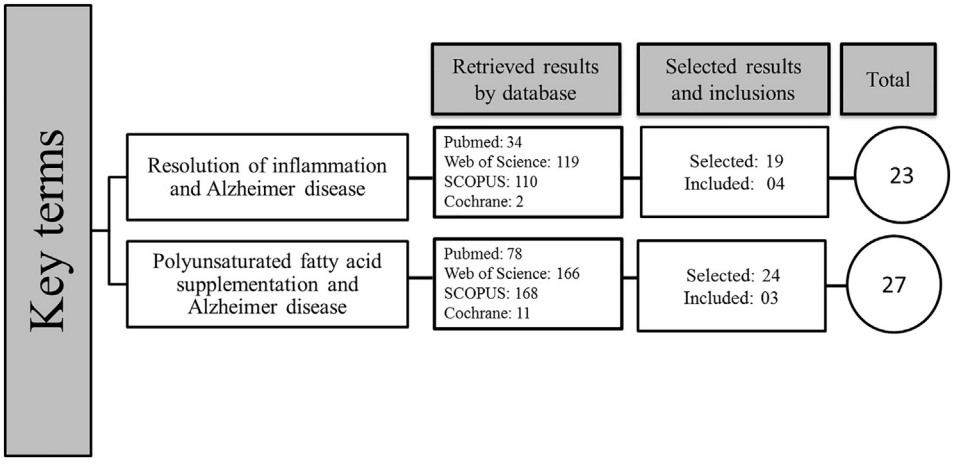

Fig. 1. Description of systematic search in literature.