Ageing Research Reviews 12 (2013) 174–181

Contents lists available at SciVerse ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

Viewpoint: Crosstalks between neurofibrillary tangles and amyloid plaque formation

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ARTICLE INFO

Article history:
Received 23 February 2012
Received in revised form 17 May 2012
Accepted 6 June 2012
Available online 19 June 2012

Keywords:
Alzheimer's disease, Tau kinases, Amyloid plaques

ABSTRACT

Since its discovery, the hallmarks of Alzheimer's disease (AD) brain have been recognised as the formation of amyloid plaques and neurofibrillary tangles (NFTs). Mounting evidence has suggested the active interplay between the two pathways. Studies have shown that β-amyloid (Aβ) can be internalized and generated intracellularly, accelerating NFT formation. Conversely, tau elements in NFTs are observed to affect Aβ and amyloid plaque formation. Yet the precise mechanisms which link the pathologies of the two brain lesions remain elusive. In this review, we discuss recent evidence that support five putative mechanisms by which crosstalk occurs between amyloid plaque and NFT formation in AD pathogenesis. Understanding the crosstalks in the formation of AD pathologies could provide new clues for the development of novel therapeutic strategies to delay or halt the progression of AD.

1. Introduction

Since its discovery in 1906 by Dr. Alois Alzheimer, AD has been recognized to consist of two pathological hallmarks: extracellular amyloid/senile plaques (SPs) and intracellular neurofibrillary tangles (NFTs; Alzheimer, 1907). Aβ has been identified as the major component of SPs (Glenner and Wong, 1984) while hyperphosphorylated tau constitute NFTs (Delacourte and Defossez, 1986). The debate to determine which protein aggregate played a more primal role in AD pathogenesis has split the AD research community and led to the articulation of two primary hypotheses.

The first theory to fully explain the formation of both pathological hallmarks, formulated in 1992, was the amyloid-cascade hypothesis (ACH; Hardy and Higgins, 1992). The ACH proposed that progressive Aβ generation, deposition and accumulation occurred upstream of plaque and tangle formation. The discovery of genetic mutations that were responsible for autosomal dominant familial AD capitulated Aβ as the "signature" protein of AD (Glenner and Wong, 1984). However, removal of Aβ did not halt AD pathology, which suggested that ACH alone is not sufficient to explain AD pathology.

The second hypothesis proposed that mechanisms which induce tau hyperphosphorylation play a far more significant role in AD pathology (Cleveland et al., 1977 and reviewed in Susanne et al., 2011). The hyperphosphorylation of tau would increase its tendency to aggregate and further promote the formation of paired helical filaments (PHFs) which would evolve into NFTs (Grundke-Iqbal et al., 1986). The role of tau in AD seemed critical as tau phosphorylation of specific residues within tau dramatically affects its ability to bind to and stabilize microtubules (Iqbal et al., 2005). Early studies demonstrated that disrupted microtubule systems in AD infected neurons were replaced by PHF-NFTs and it was suggested that destabilization of the neuronal cytoskeleton may play a critical role in the pathogenesis of AD (Iqbal and Grundke-Iqbal, 1996). Tau hyperphosphorylation depends on the activities of protein kinases and protein phosphatases (Wang et al., 1995). Protein kinases are responsible for the phosphorylation of tau whereas protein phosphatases are responsible for its dephosphorylation. An imbalance in the activities of tau kinases and phosphatases may be the cause of hyperphosphorylation and subsequent NFT formation (Gong et al., 1993, 1994; Trojanowski and Lee, 1995; Morishima-Kawashima et al., 1995; Ladner et al., 1996).

As both hypotheses described above suggest primal roles for either Aβ or tau proteins in the formation of pathological plaques or tangles, intensive research efforts in AD have been greatly polarized. In this review, we suggest that various crosstalks exist between the two pathologies. Such crosstalks have received considerably less attention. In recent years, there has been increasing evidence that Aβ can be internalised or generated intracellularly, providing the opportunity for Aβ to directly or indirectly

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http://dx.doi.org/10.1016/j.arr.2012.06.002

facilitate NFT formation (LaFerla et al., 2007). Conversely, tau pathology can affect the formation of Aβ and subsequently, amyloid plaque formation (Blurton-Jones and LaFerla, 2006; Mazzitelli et al., 2011).

2. Aβ trafficking

Amyloid precursor protein (APP), a transmembrane protein that is abundantly localised in the plasma membrane, is sequentially cleaved by β-site APP-cleaving enzyme 1 (BACE1) and γ-secretases in AD brain to form the amyloidogenic Aβ peptide (reviewed in LaFerla and Oddo, 2005). Cleavage by β-secretase releases a soluble N-terminus APPβ (sAPPβ) into the extracellular space. The remaining 99 residue C-terminal (C99) in the plasma membrane is further processed by γ-secretase at the C-terminal region of the Aβ sequence, resulting in the formation of Aβ and a C-terminal peptide containing 50 residues. Aβ is released into the extracellular space where it accumulates and contributes to amyloid plaque formation while the remaining 50 residues in the C-terminal, which is known as the APP intracellular domain (AICD), is released intracellularly (LaFerla and Oddo, 2005).

APP is also embedded within membranes of intracellular organelles, including the golgi, endoplasmic reticulum (ER), endosome, and mitochondria (Mizuguchi et al., 1992), where it can be processed into Aβ (reviewed in LaFerla et al., 2007). The first evidence that Aβ is generated not only in the plasma membrane but also intracellularly was observed in human NT2N cells (Wertkin et al., 1993). This finding was supported by a report that although β and γ-secretases are largely localized in the plasma membrane, they are also present in intracellular membranes as noted in human neuroblastoma SHEP cells and in mouse Neuro-2a cells (Yan et al., 2001), allowing for internal cleavage of APP and generation of Aβ.

The internalization of APP by endocytosis is an important pathway for the intracellular generation of Aβ (Fig. 1). This was evident when blocking APP internalization caused a significant decrease in intracellular Aβ levels (Koo and Squazzo, 1994). It is believed that the C-terminal motif may act as a signal for APP internalization (Zhongtao et al., 1997). When APP is internalized into early endosomes, it is recycled to the golgi in the presence of sortilin related receptor (SORL1). APP in the golgi can also be cleaved by β and γ-secretases to form Aβ. Under fluorescence resonance energy transfer (FRET) microscopy, it was observed that when SORL1 is not present, the acidic pH of the endosome creates an optimal environment for β-secretase activity (Kinoshita et al., 2003). The resulting C99 fragment can be further processed into Aβ through four distinct pathways (Fig. 1): C99 is (i) shuttled back to the plasma membrane and cleaved by membrane γ-secretase (Cook et al., 1997; Lee et al., 1998; Wild-Bode et al., 1997), (ii) transported to the ER and cleaved by ER γ-secretase or (iii) cleaved by γ-secretase within the endosome/lysosome system. C99 on the plasma membrane can also be internalized into early endosomes and processed into Aβ through these three pathways. (iv) If C99 is not cleaved by ER γ-secretase when it is transported to the ER, it can be transported to the golgi where it is cleaved by golgi γ-secretase and processed into Aβ (Hartmann et al., 1997). Aβ generated intracellularly along the secretory ER/golgi pathway is secreted into the extracellular space where it contributes to amyloid plaque pathology (Busciglio et al., 1993).

Extracellular Aβ can also be internalized *via* endocytosis through the Aβ-receptor complex (Fig. 2; Koo and Squazzo, 1994; Bu et al., 2006; Deane et al., 2003; Nagele et al., 2002; Yazawa et al., 2001). Extracellular Aβ, which binds to cell surface receptors (7 nicotinic acetylcholine receptor, 7nAChR; N-methyl-D-aspartate, NMDA; and receptor for advanced glycation end products, RAGE), causes rapid endocytosis of the Aβ peptide-receptor complex into early endosomes. Upon entry into the endosome/lysosome system, Aβ is released into the intracellular environment.

Internalized extracellular Aβ and Aβ generated intracellularly results in the intracellular accumulation and aggregation of Aβ. This allows for the direct interaction of the peptide with intracellular proteins involved in NFT formation, thereby allowing crosstalks between amyloid plaque and NFT formation. These include Aβ-induced tau hyperphosphorylation, mitochondria dysfunction and proteasome dysfunction.

3. Mechanistic links between plaque and tangle formation

Based on previous studies, we postulate five major crosstalk pathways in the pathogenic formation of amyloid plaques and NFTs in AD (Fig. 2). In three of these pathways, Aβ facilitates tau pathology (Fig. 2, red lines). First, Aβ activates tau kinases which induce NFT formation *via* (a) tau hyperphosphorylation and (b) tau axonal transport deficits. Aβ upregulates the activity of tau kinases through four separate pathways (summarized in Fig. 3), inducing tau hyperphosphorylation and subsequent NFT formation. Oligomeric Aβ activation of tau kinase GSK-3β induces GSK-3β phosphorylation of the kinesin light chain (KLC), the altered deposition of tau and subsequent NFT formation. Second, Aβ-mediated proteasome dysfunction decreases tau degradation, increases tau aggregation and induces NFT formation. Third, Aβ activation of caspase-3 causes tau truncation and altered tau aggregation which promotes NFT formation. In the other two major pathways, plaque formation is affected by tau-related pathways (Fig. 2, blue lines). Fourth, tau kinases alter APP processing and Aβ formation by phosphorylating APP and activating γ-secretase. Further phosphorylation of Aβ by tau kinase PKA promotes aggregation and the formation of Aβ oligomers. Fifth, inhibition of tau degradation causes tau to compete with kinesin to bind to microtubules, APP axonal transport deficits and altered APP production which promotes amyloid-plaque formation.

3.1. Upregulation of tau kinases by Aβ

3.1.1. NFT formation through tau hyperphosphorylation

Aβ can directly or indirectly upregulate tau kinases through four distinct pathways (Fig. 3). These include Aβ-mediated (i) cell receptor signalling, (ii) mitochondria dysfunction, (iii) inflammation and (iv) c-Abl activation. The upregulation of tau kinases by Aβ-induced signalling pathways are responsible for the abnormal phosphorylation of tau in AD.

Cell receptor signalling: When Aβ binds to neurons, membrane receptors (p75 neurotrophin receptor, p75NTR; alpha 7 nicotinic acetylcholine receptor, α7nAChR; formyl-peptide receptor-like-1, FPRL1; N-Methyl-D-aspartate receptor, NMDAR and RAGE) cause activation of various signaling pathways that involve the tau kinases, Cdk5, GSK3β, and p38MAPK (Balleza-Tapia and Peña, 2009). While the Aβ-p75NTR complex stimulates JNK activity, the Aβ-α7nAChR complex induces GSK-3β and JNK activities, and the Aβ-NMDAR complex stimulates p38MAPK activity (Texidó et al., 2011). On the other hand, Cdk5 activity is upregulated when Aβ binds to NMDAR, α-nAChR, p75NTR and FPRL1R (Texidó et al., 2011). In this process, intracellular Ca^{2+} enhances the activity of calpain (Higuchi et al., 2011), which converts p35 to p25, a potent activator of Cdk5 that has a longer half-life than p35, causing elevated Cdk5 activity (Lee et al., 1999; Nguyen et al., 2002; Peterson et al., 2010). Increased intracellular Ca^{2+} levels also promote reactive oxygen species (ROS) production and subsequently, Cdk5, JNK and p38MAPK activity (Mattson and Goodman, 1995). Similarly, ROS-induced upregulation of Cdk5, JNK and p38MAPK occurs when