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Chapter 3

Neuroinflammation and Alteration of the Blood-Brain Barrier in Alzheimer´s Disease

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1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disease, characterized by progressive memory loss, cognitive deterioration and personality changes. Neuropathologically AD brains are characterized by massive accumulation of neurofibrillary tangles (NFT). NFTs are composed by paired helical filaments (PHF), which main constituent is tau protein. Another hallmark lesions of AD are Neuritic plaques (NPs), constituted by extracellular amyloid peptide aggregates (Aβ), that are associated with distrophyc neurites (DNs). Amyloid precursor protein (APP) processing occurs via two pathways. A) The amyloidogenic and B) the non-amyloidogenic pathway. In the amyloidogenic pathway, the APP is proteolyzed by β-secretase. This truncation occurs at the N-terminus of APP. The cleavage produces a soluble N-terminal fragment of APP (sAPPβ) and a C-terminal transmembrane fragment (β-CTF). β-CTF is cut into the membrane by γ-secretase and generates the Amyloid beta (Aβ) peptide and the APP intracellular domain (AICD). Depending on the site of γ-secretase cleavage, two main species of Aβ are generated: Aβ 40 and Aβ 42 amino acids. Aβ 42 is more hydrophobic and more prone to aggregate, as compared to the Aβ 40 peptide. In the non-amyloidogenic pathway, APP is cleaved by the α-secretase. This cleavage occurs in the middle region of Aβ and produces an N-terminal fragment of soluble APPα (sAPPα) and a C-terminal transmembrane (α-CTF) fragment. The sAPPα have neurotrophic and neuroprotective functions.

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Similarly to β-CTF, α-CTF after being cleaved by γ-secretase generates a 23-25 amino acid peptide designated as p3. Aβ aggregates promote an inflammatory response mediated by activated microglia and astrocytes, that may activate pathological signalling pathways, leading to neurodegeneration. Long-term activation of the innate immune system is able to trigger an inflammatory cascade that converges on alterations of the cytoskeleton (including aggregation of tau protein and formation of PHFs and microtube disassembling) promoting neuronal degeneration. One of the pathological signalling pathways that may lead to neurodegeneration is oxidative stress, defined by the generation of a large amount of reactive oxygen species (ROS), which are highly harmful since they lead to the alteration in the structure of proteins, lipids and nucleic acids and cellular death. High levels of copper and iron have been detected in the blood plasma of people with AD. These metals catalyse the production of ROS by the Fenton reaction resulting in the generation of highly reactive hydroxyl radical, so that the reactivity of these metals can give rise to cellular damage and neurodegeneration. In AD, it had been described oxidative stress caused by free radicals (FRs). The most important in human biology FRs are superoxide (O_2 -), hydroxyl (OH·), nitric oxide (NO·), and trichloromethyl (CCl_3·). In AD, there is an increase in iron concentration in the hippocampus. There is an accumulation of iron and aluminum in NPs and cerebrospinal fluid (CSF), which could contribute to this oxidative stress. In AD, neuroinflammation is involved in multiple pathological mechanisms. Clinicopathological and neuroimaging studies have shown that inflammation and microglial activation precede neuronal damage and that oxidative stress occurs prior to neurodegeneration. Aβ accumulation alters the normal neuronal function, cell death, even before the formation of NPs and NFTs. Aβ not only has been linked to the inflammatory response, but also in a lesser extent to tau pathology. The Aβ itself causes activation of microglia and astrocytes through toll-like receptors 2, 4, 9 (TLR); activated microglia produces neurotoxic molecules and is conveniently located to the vicinity of the NPs. The proinflammatory cascade generated by microglial activation, results in the release of cytotoxic molecules such cytokines, chemokines, matrix metalloproteinases, and complement factors. These cytotoxic molecules may enhance neuronal neurodegeneration increasing sensitivity to FRs. The neurotoxicity mediated by microglial cells depends on ROS and cytokines. The present chapter address the physiological and pathological role of proinflammatory cytokines and the induction of tau pathology including tau accumulation and the formation of NFTs, as well as the mechanisms involving extracellular deposits of beta amyloid species (Aβ1-42, Aβ1-40, Aβ3-42 and Aβ11-42), which generate neurotoxic microenvironment in AD. In relation with the mechanisms involved in AD neuroinflammation, we will discuss the participation of caspases in inflammation and its likely activation as a result of the accumulation of endothelial cells. We will also talk about how the accumulation of Aβ in blood vessels affects blood-brain barrier endothelial cells tight junctions, modifying its permeability and its implications in AD pathology.

2. Diagnosis of Alzheimer's disease

AD can be diagnosed with 70% of accuracy, with a battery of clinical analysis and cognition tests. However, the definitive diagnostic test for AD is done post-mortem through histological analysis of the brains of patients.

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2.1. Gross microscopy pathology

Atrophy of the brain in a case of AD, is generally symmetrical and diffuse in the convolutions, which is evidenced by the decrease in thickness. An increase in the depth of the grooves, a dilatation of the ventricles (Fig 1A and B compared to Fig 1 C and D) and decreased brain weight and volume is noticeable. Atrophy, mainly affecting the hippocampus, and the adjacent area transenthorinal, entorhinal cortex and the temporal and frontal lobes (Fig 1 C,D).

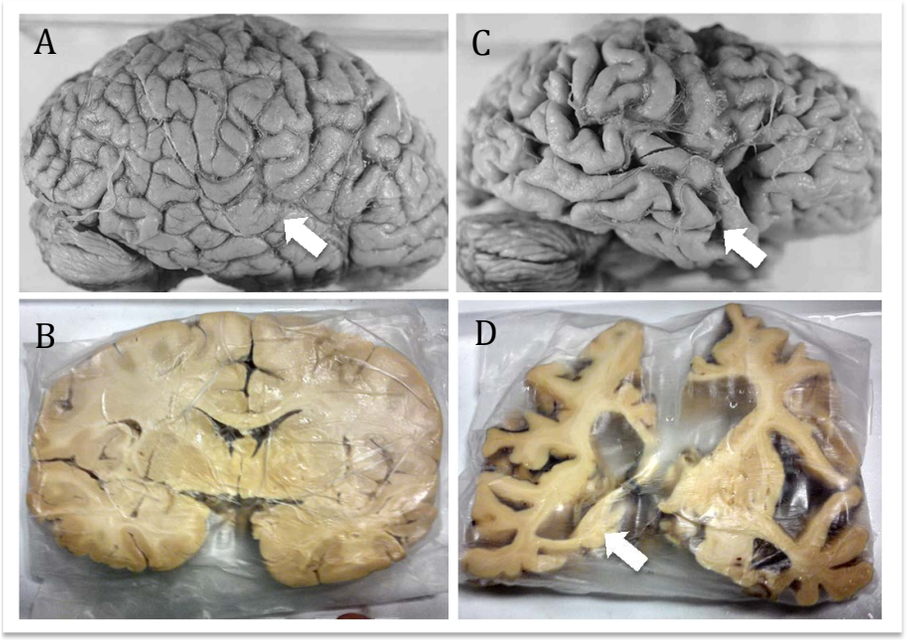


Figure 1. Neuroanatomical comparison of normal brain and Alzheimer´s disease brain. A,B) Normal Brain. C,D) Brain with pathology of AD. B) Prominent atrophy seen in fronto-temporal areas involved with association functions (arrows). B, D) Coronal sections of A) and C) respectively. Where observe an enlargement of the ventricles and selective hippocampal atrophy (arrow).

2.2. Histopathology of Alzheimer's disease

Microscopically, AD is characterized by the presence of lesions in the brain tissue known as neurofibrillary tangles (NFTs. Fig. 2 A, B. long arrows), dystrophic neurites (DNs. Fig. 1 C short arrows) and neuritic plaques (NPs, Fig. 1. C).

2.3. Neurofibrillary tangles

It has been shown that the severity of dementia in AD, correlates significantly with the density of NFTs in the neocortex and entorhinal cortex [1, 2]. At the stage of degeneration NFTs may be intracellular (iNFT, Fig. 2A) or extracellular (eNFT, Fig. 2B), [3] The formation of NFTs is associated with neuronal death [4-6] and found a strong correlation between neuronal degeneration and the transition between iNFT and eNFT [7]. The iNFT are characterized by a compact consistency and to be able to distinguish the cell membrane and the nucleus, although the nucleus may be displaced from its original position by the inclusion of fibrils. NFT is such

a typical flame shape (Fig.2A). The eNFT show a fibrillar relax form and without nucleus (Fig 2B). These eNFT, are considered as the "skeleton" or "ghost" of the affected neuron (Fig 2B), are released into the extracellular space as a consequence of cell death, which remain stable due to its high insolubility and resistance to proteolysis.

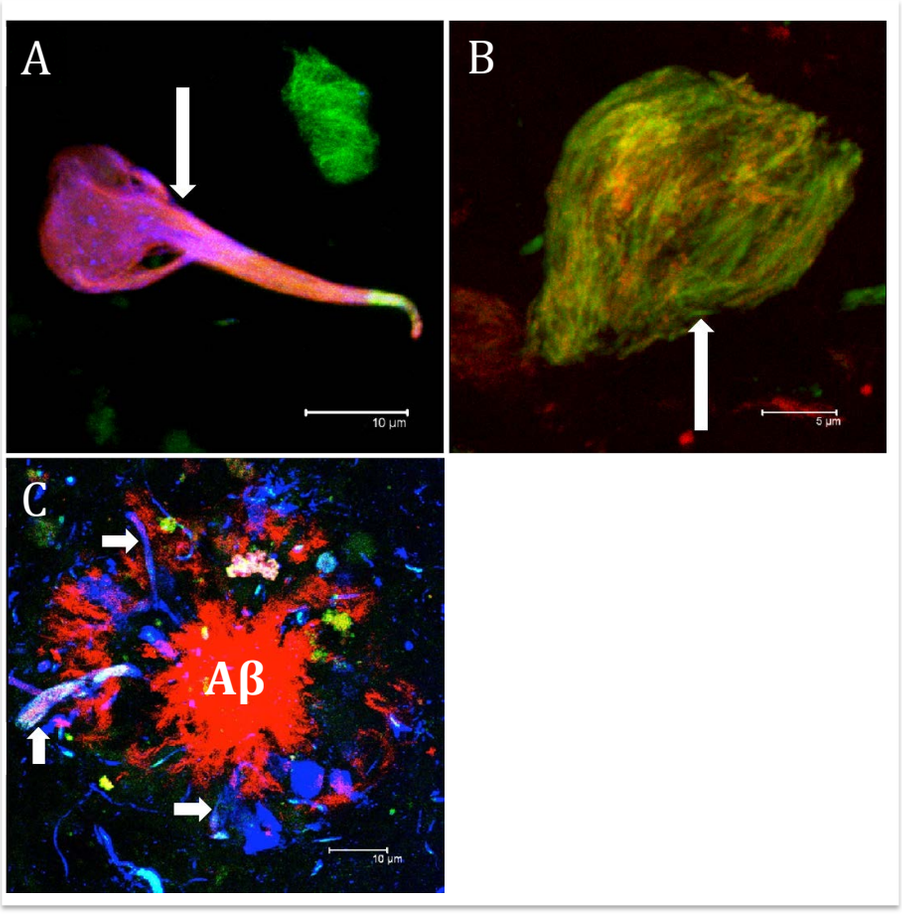


Figure 2. Hallmark characteristic of Alzheimer's disease brains. A) intracellular neurofibrillary tangle B) extracellular neurofibrillary tangle, are evidenced with antibodies against protein tau. C) Neuritic plaque. Evidenced by thiazine red dye (red channel) marker of beta-pleated sheet conformation and doble immunolabelling with two antibodies raised against tau protein to evidence dystrophic neurites (arrows), associated with these beta amyloid deposits (Aβ). Confocal microscope images (Leica SP8).

3. The tau protein and paired helical filaments

The NTFs and DNs (a component of NPs) are formed by the accumulation of abnormal polymers know as paired helical filaments (PHFs), due to their ultrastructural appearance [8]. The PHFs are characterized by its staining with thiazine red fluorescent dye, which has affinity for β-pleated structures [9], and have been used to differentiate between non-fibrillar (pre-assembled) amorphous and fibrillar states (assembled) of tau protein in AD [3, 10]. The main structural constituent of PHFs is tau protein, which is normally associated with microtubules.

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3.1. Tau protein structure

Tau is the major component of the family of microtubule-associated proteins in the neuron. The tau gene was located on the long arm of chromosome 17 (17q21) and contains 16 exons[11]. Three of these exons (exon 4, 6 and 8), occurs only in the peripheral tissue RNA and these are not present in human brain mRNA, exons 1 and 14 are transcribed but not translated [12-15]. Exons 2, 3 and 10 have an alternative splicing and exon 3 never appears in the absence of exon 2 [15, 16]. Alternative splicing of three exons latter produces six isoforms of tau protein in the adult brain [12, 17]. Tau isoforms differ from each other by the presence or absence of one or two inserts (29 or 58 amino acids) in the amino terminal portion and by the presence of 3 to 4 repeated domains in the carboxyl terminal portion. The length of the various isoforms of tau varies from 352-441 aa's (Fig 3) [18].

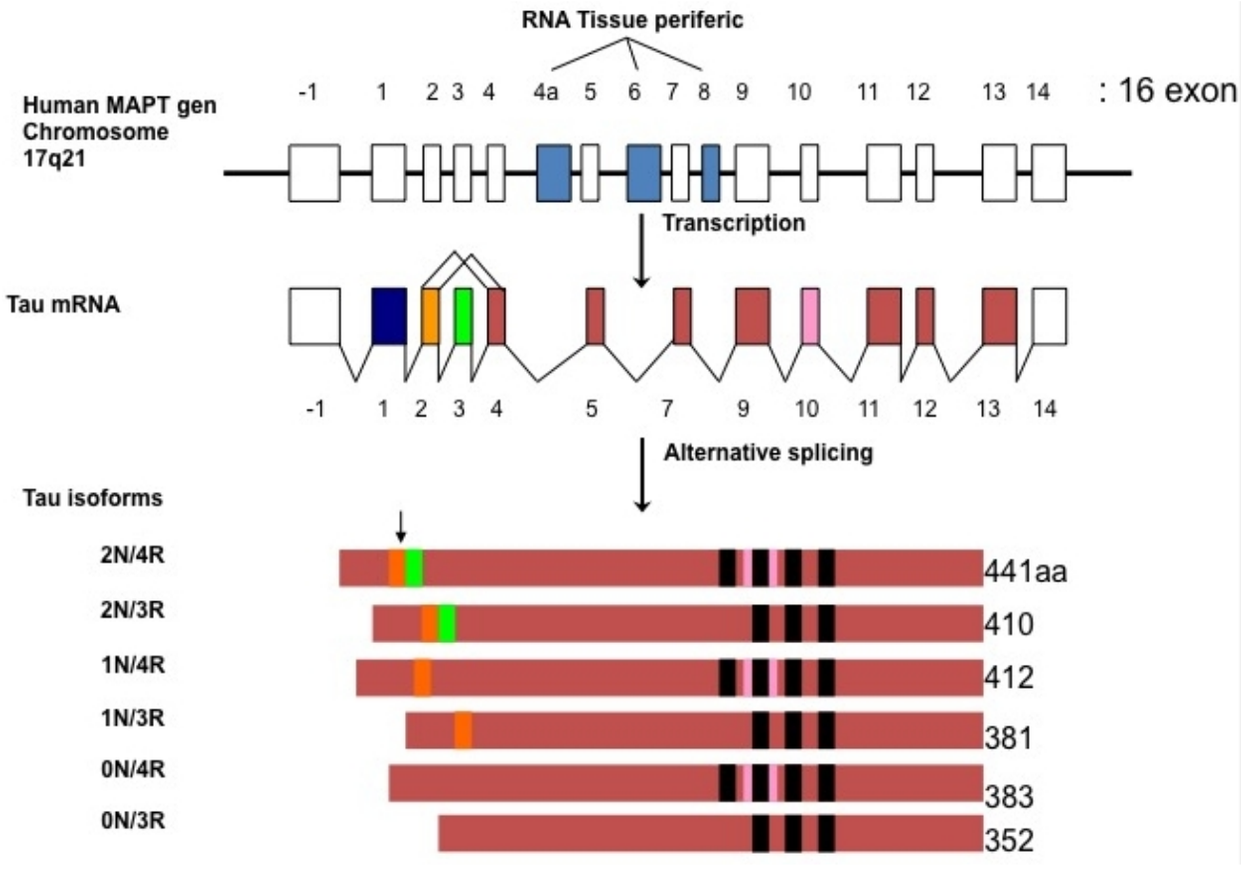


Figure 3. Schematic representation of tau protein gene. The MAPT gene encoding the tau protein is located on chromosome 17q21, which contains 16 exons. Isoforms of tau protein in human brain is encoded by 11 exons. Exons 2, 3 and 10 are alternatively spliced, favouring the synthesis of 6 isoforms. With a range of longitude between 352-441 amino acids. They differ by the presence or absence of one or two inserts of 29 amino acids at its amino terminal portion and by the presence of 3 or 4 microtubule binding domains in its C-terminal portion.

3.2. Post-translational modifications of tau protein in AD

It has not been reported for AD any change in the levels of RNAs messenger of any of the existing six isoforms of tau protein, which suggested, from the beginning, that abnormal forms of the protein found in PHFs originate from posttranslational modification rather than the novo synthesis [12]. There are two posttranslational modifications of tau protein, as the major molecular mechanisms involved in the pathophysiology of AD: the abnormal hyperphosphorylation and endogenous proteolysis [19, 20]. Both pathological processes are involved in the cascade of molecular events that lead to irreversible polymerization of tau protein into PHFs. Recently it has been described a series of tau conformational changes which appear to be associated, in fact, they appear to be the consequence of both the endogenous hyperphosphorylation and the truncation [21, 22].

4. Neuritic plaques

NPs are composed of extracellular deposits of insoluble amyloid fibrils that are made-up of Aβ peptide (Fig 2C), and these deposits are associated with neuritic component from dendritic and axonal origin (Fig. 2B arrows). There could also be AD brains with soluble non-fibrillar β-amyloid deposits without DNs associated, named senile plaques (SPs). SPs do not have a selective topographic distribution, however, their density is predominant in motor or sensory cortical areas than in primary hippocampal. The density of NPs in AD, in general, does not have a good correlation with the progression of dementia and the degree of neuronal loss [5, 23].

5. Amyloid precursor protein and amyloid-β peptide

Aβ originates from a large trans-membrane molecule, called APP. So far 8 isoforms of APP are known, were the predominats are the ones of 695, 751 and 770 aa's. The 695 isoform is the most abundant neuronal isoform. APP is a membrane glycoprotein with a single transmembrane domain, an intracytoplasmic portion and a extracellular long portion (Fig. 4). APP has an hydrophobic region of 23 aa's, by which it is anchored to cell membrane. The extracellular domain exposed to partial proteolysis by the action of three secretases (α, β and γ) (Fig 4). The proteolytic processing of APP, can occur via two types: the amyloidogenic and the non-amyloidogenic. By the action of both enzymes: γ (presenilin 1) [24] and β (transmembrane aspartyl protease called BACE) secretases, fragments of Aβ are generated, predominantly the fragments of 40 and 42 aa's. Alternatively to this proteolytic pathway amyloidogenic form, the action of α-secretase (metallo-protease and call disintegrin TACE) that cleaves the sequence of Aβ at aa's 16 and 17, represents a non-amyloidogenic processing. At first it was thought that the Aβ was produced only in pathological events, however, it was demonstrated that its production and secretion are physiological process, and Aβ is present in plasma and cerebrospinal fluid during the normal life of an individual [9, 25, 26]. In AD, APP metabolism is altered with a progressive increase in the production and abnormal deposition of Aβ. There are some Aβ deposits without neuritic component in elderly individuals without cognitive impairment

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[27]. In general, it is thought that the abnormal accumulation of Aβ may be depend on certain alterations in the normal metabolic APP processes. Recent studies have emphasized a neurotoxic role of Aβ in *in vivo* animals models, which have led to reconsider the Aβ peptide, as one of the main factors related to the molecular pathogenesis of AD [28-30].

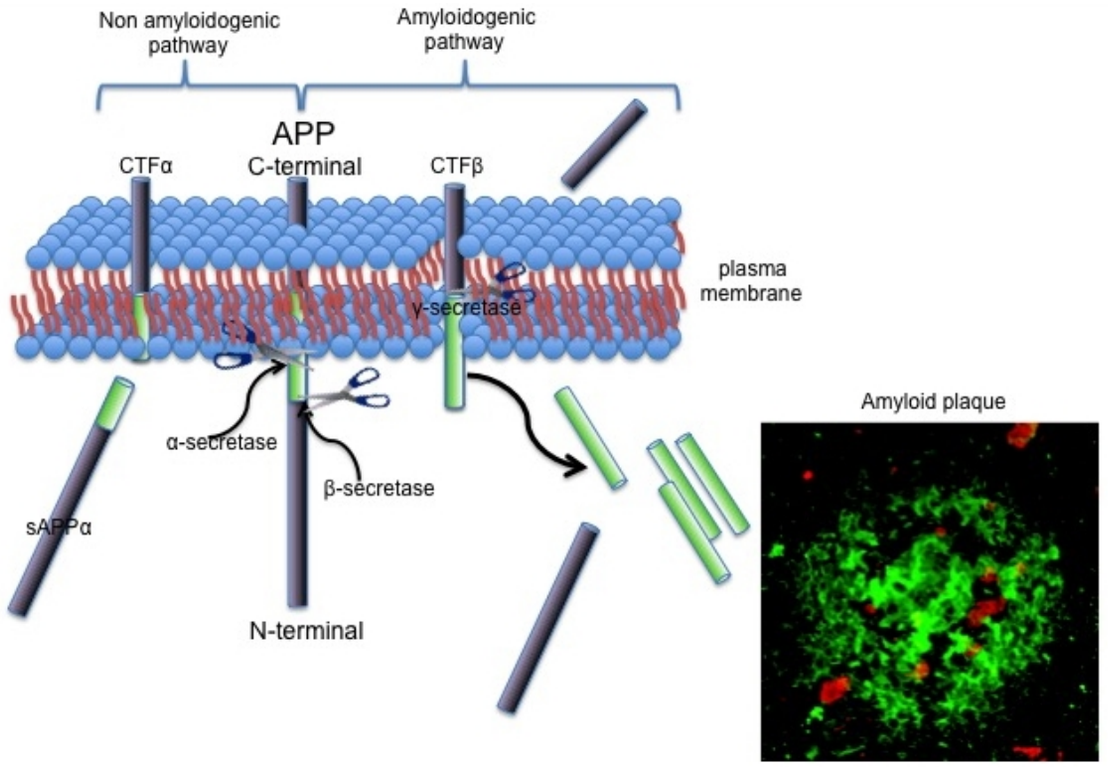


Figure 4. Amyloid precursor protein structure and metabolism. Schematic representation of APP processing by α-, β-, and γ-secretases. APP processing by secretase activities is divided into the non-amyloidogenic pathway on the left and the amyloidogenic pathway on the right. α- and β-secretase activities cleave APP in its extracellular domain to release respectively a soluble fragment sAPPα or sAPPβ in the extracellular space and generate carboxy-terminal fragments CTFα or CTFβ. These CTFs can subsequently be processed by γ-secretase complex to generate AICD and Aβ. The γ-secretase complex is composed of presenilin, nicastrin (NCT), γ-secretase activating protein (GSAP), pen-2, and aph-1.

6. Oxidative stress and Aβ

It is known that Aβ aggregates promote an inflammatory response, mediated mainly by microglia and astrocytes, which activate pathological signaling pathways, which may lead to neurodegeneration. A long-term activation of the innate immune system, is a mechanism capable of triggering an inflammatory cascade that culminates in cytoskeletal alterations (tau aggregation and formation of PHFs) with neurodegenerative consequences of this hypothesis, it has named "neuroimmunomodulation" [31].

One of these pathological signalling pathways that may lead to neurodegeneration, is oxidative stress, defined as the generation of a large amount of reactive oxygen species (ROS), which are highly harmful, leading to the alteration in the structure of proteins, lipids and nucleic acids

and cell death [32]. AD described in the oxidative stress caused by free radicals (FRs). Major FRs in human biology are superoxide (O_2 -), the hydroxyl (OH ·), nitric oxide (NO ·), the thiyl (RS ·) and trichloromethyl (CCl_3 ·). There seem to be an accumulation of iron and aluminum in NPs and CSF [33], which could contribute to this oxidative stress [34].

Under physiological conditions, Aβ could regulate the release of NO, neurotransmitters, and hormones, long term potentiation and promotes cell survival. High levels of NO are generated under conditions of inflammation and may contribute to synaptic dysfunction, oxidation of proteins and lipids; culminating in neuronal death [35, 36] (Figure 5).

In AD, it has been shown that the A ▪ -peptide is able to promote the production of NO in microglia and activated astrocytes [37, 38] the release of proinflammatory cytokines such as IL-1β and TNF-*α* which contribute to the formation of NO and peroxynitrite [38, 39] and cause changes in proteins and lipids, mitochondrial damage, apoptosis and promotes the formation of Aβ, as well as increasing γ-secretase activity [40, 41] (Figure 3, 5). NO synthesis during development of AD could also contribute to the formation of NFTs (Fig 5), favouring the increase of tau phosphorylation [42].

7. Neuroinflammation as a trigger of neuronal death

Inflammation is involved in many pathological mechanisms in AD [43]. Clinicopathological and neuroimaging studies show that microglial activation and inflammation precede neuronal damage [44], and oxidative stress occurs before the histopathologycal lesion of AD appear [45]. But inflammation can be neuroprotective in its early stages [46] and the inability to resolve the activating stimulus can result in a chronic inflammatory response.

Under physiological conditions, glial cells and neurons express cytokines involved in modulating various functions including cellular homeostasis, metabolism, synaptic plasticity, and neural transmission. The Aβ plays a role in synaptic function and pathology [47], inducing degeneration, promoting the release of excitatory neurotransmitters by increasing intracellular calcium and ROS production (Figure 4) [48]. Aβ accumulation in the brain parenchyma and blood vessels promote microglial migration causing chronic and acute inflammatory response and induces production of FRs, proinflammatory cytokines and prostaglandins (PG), which may eventually promote neuronal death [49]. Aβ accumulation could disrupt the normal operation of the neurons, resulting in a significant cell dysfunction, which leads to apoptosis even before the formation of NPs and NFTs.

8. Glial cells key mediators of the inflammatory response in AD

Microglia cells are derived from monocytes during embryogenesis and are responsible for neuronal damage response [49]. Functions related to the immune response participate in a variety of neuroinflammatory processes [50].

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The inflammatory response in AD includes morphological changes of microglia cells ranging from a branched cell "inactive" to the amoeboid appearance "active" [51, 52]. Activated microglia expresses several molecules on their surface, such as: Fc receptors required in phagocytosis of opsonized antigens by IgG, scavenger receptors *[53]*, cytokine and chemokine receptors, complement receptors as CD11b, CD11c, CD14, molecules of the major histocompatibility complex (MHC) [54], Toll-like receptors (TLR) family and Aβ receptors as the receptor for advanced glycation endproducts (RAGE). Cell surface microglial receptors are required for interaction with different types of immune cells, molecules involved in inflammatory responses in the brain and Aβ [55-57].

Aβ itself, causes activation of microglia and astrocytes through TLRs 2, 4 and 9 [54], when activated microglial cells produces neurotoxic molecules and strategically are located in the vicinity of the NPs. This proinflammatory cascade generated by microglial activation results in the release of cytotoxic molecules such as interleukins (IL-1 α, IL-1 β, IL-6, IL-10, IL-12, IL-16, IL-23), growth factors (transforming growth factor beta. TGF-β), chemokines, metalloproteinases (MMP-2, MMP-3, MMP-9), eicosanoids (PGD 2, leukotriene C4, cathepsins B and L) and complement factors (C1, C3, C4) also causing astrocytes chemotaxis around NPs [52]. Activated microglia also releases excessive amounts of glutamate and thereby inducing neurodegeneration These molecules can enhance cytotoxic neurodegeneration, increasing sensitivity to FRs [39]. Thus microglia-mediated neurotoxicity depends on ROS and cytokines [58, 59].

9. Astrocytic activation and their significance in the AD

Astrocytes represent the most abundant glial cell type in the CNS. They provide physical and metabolic support for neurons, and they are involved in the formation and maintenance of the BBB (Fig 5A), they produce neurotrophic and neuroprotective factors and are involved in repair processes within the CNS [60]. Attenuate the production of FRs and tumor necrosis factor α (TNF-α) [61], reduces microglial activation by Aβ [62] and alter their phagocytic activity [63]. They also decrease the cytotoxicity of A ▪ , both directly and indirectly through modulation of microglial cells [64].

In early stages of AD, activated astrocytes are located in two areas: in the molecular layer of the cerebral cortex and the amyloid deposits below the pyramidal cell layer. The activated astrocytes can phagocyte and degrade Aβ, suggesting that these cells are very important in the removal of parenchymal Aβ aggregates (Fig 5A and 6A. Arrowheads). As microglia, astrocytes are also activated by TLRs dependent pathways and RAGE receptors, therefore causing local inflammation and eventually favouring neuronal death [49]. Activated astrocytes produce numerous pro-inflammatory molecules as microglia, but unlike microglia, astrocytes produce S100β, which is highly expressed in the proximity of the Aβ deposits. Prolonged activation of astrocytes has a detrimental impact on neuronal survival and S100β could exacerbate this effect [65].

10. Monocytic cells derived from bone marrow function as a compensatory mechanism to remove amyloid deposits

There are 2 types of phagocytic cells within the CNS that are capable of initiating the innate immune response: microglia and peripheral macrophages [66]. These macrophages are recruited into the CNS by cytokines and chemokines, which are released during the microglial and astrocyte activation able to cross the blood brain barrier (BBB) [49]. Cells derived from bone marrow, can cross the BBB into the CNS and differentiate into microglia, which are located surrounding the amyloid deposits [67, 68]. This finding is very important, since if the resident activated microglia is incompetent to eliminate amyloid deposits, macrophages from the periphery could remove them by phagocytosis [69].

The presence of microvasculature in the brain promotes the release of chemokines such as IL-8, MPC-1, MIP-1, MIP-1α and MIP1-β and thereby promoting differentiation of monocytes into macrophages and migration through the BBB [70]. Analysis of the cerebrospinal fluid (CSF) of AD patients showed an increase in the levels of chemokines such as MCP-1 and IL-8 [71, 72]. In vitro models have demonstrated the ability of (CD4 and CD8) lymphocytes to cross the BBB [73] by increasing the level of MIP-1α.

11. Effect of neuroinflammatory environment on BBB integrity

In AD brains, it has been observed a number of inflammatory reactions, surrounding brain microvasculature, together with A ▪ accumulation, which is associated with a dysfunction of the BBB. Morphological the BBB consists mainly of vascular endothelial cells, and other cellular components secondarily supporting the BBB that include pericytes found in the abluminal basal lamina, the perivascular astrocyte that form extensions towards capillaries around the basal lamina of the capillary wall and microglia.

The permeability and integrity of the BBB is regulated by the endothelial intercellular tight junctions (TJ), that consists of three integral membrane proteins: claudin, occludin and adhesion juntion molecules, as well as some accessory cytoplasmic proteins (ZO1, ZO2, ZO3 and cingulin). Cytoplasmic proteins are linked to actin cytoskeleton primary protein essential for the structural and functional maintenance of the endothelium [74]. While adherent junctions are formed by Vascular endothelium cadherin (VE-cadherin) which is a transmembrane glycoprotein catenin that its main function is to anchor the complex of cadherins and thereby the actin cytoskeleton, but also it is involved in the development of cellular signalling pathways (Figure 5) [75].

During neuroinflammation, leukocytes can infiltrate the brain microenvironment generating high levels of inflammatory mediators such as TNF-α and IFN-γ [76]. Increased levels of TNF-α had been reported not only in endothelial and TJ modulating cytoskeletal rearrangement of brain endothelial cells (BEC) [77, 78], but also by causing an increase in the production of caspase-3 leading BEC to apoptosis [79]. However activation of this caspase 3, not always leads

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to apoptosis [80] and it has been shown that hypoxia can induce activation of caspases 3 and 9, without inducing neuronal apoptosis [81]. The caspase-3 has been involved in the disassembly of ZO-1 and claudin-5 in TJ regardless of fragmentation during cerebral ischemia (Fig. 5. blood Vessel) [82].

A recent study showed that TNF-α alone or in combination with IFN-γ induces hypermeability, causing the leak of paracellular tracers and also induce degradation of ZO-1. Alterations in the function of brain endothelial cells (BEC) could lead to BBB breakdown, due to high concentrations of cytokines that correlates with expression of caspases 3 and 7 through activation of JNK signalling pathway and protein kinase C (PKC) and an increase in the number of apoptotic cells[83]. Treating peripheral microvascular endothelium with high concentrations of TNF-α and IFN-γ results in a loss focal intercellular adhesion mediated by VE-cadherin generating endothelial rupture areas [76] whereas low concentrations of cytokines, also led to effector caspase activation, increased paracellular flux, and redistribution of zonula occludens-1 and VE-cadherin but failed to induce apoptosis. It was also suggested that cytokines have a dose dependent effect on the BEC. The BEC exposed to high levels of cytokines may be susceptible to caspase-mediated apoptosis and the BEC exposed to low concentrations of cytokine does not undergo apoptosis but results in alterations of the BBB [83].

12. Disruption of the blood-brain barrier as a marker of AD and other dementias

BBB dysfunction is a marker of neuroinflammatory diseases [84]. The BEC are the first physical barrier and expresses CNS binding complexes including TJ, and Adherent Junctions (AJ) [85]. In active inflammatory lesions, focal BEC show abnormalities in the distribution of occludin and ZO-1, including the absence or diffuse immunoreactivity at junctions and an increased immunoreactivity in the cytoplasm [86].

Occludin is vulnerable to the attack of matrix metalloproteinase (MMPs) [87]. MMPs can degrade the basal lamina proteins like fibronectin, laminin, and heparan sulfate after ischemic injury, which helps to break the BBB [88, 89]. It was demonstrated in a study the accumulation of occludin in neurons, astrocytes and microglia in AD, frontotemporal dementia (FTD) and vascular dementia (VaD) [90], suggesting a new function of occludin and proteins of the TJ in the pathogenesis of these dementias.

In this same study it was found that claudin 5 is degraded by MMP2 and MMP9 after ischemic damage, and therefore claudin and occludin were found surrounding astrocytes, but not in brain endothelium after an alteration in the BBB [91]. It is likely that the increase in occluding levels found in astrocytes and neurons in VaD, AD and FTD [90], may be a response to autophagy of TJ proteins by these cells after the rupture of the BBB caused by chronic hypoxia, aberrant angiogenesis or both [92].

13. Blood-brain barrier mechanisms of transport and regulation of brainAβ levels

According to the neural theory, Aβ is produced locally in the brain, in contrast to the vascular theory which suggests that the origin of Aβ comes from the circulation, and that the circulation of soluble Aβ (s- Aβ) may contribute to toxicity when it crosses BEC, which compromises the BBB (figure. 3) [93]. It has been proposed that specific receptors of Aβ are present in human brain capillaries and their distribution in the BEC transport could favour the peptide coupling to the BBB [94]. These receptors include RAGE and SR [95]. It is known that both RAGE and SR are receptors with multiple functions including cell endocytosis and transcytosis of macromolecules. RAGE and SR mediate binding of sA ▪ 1-40 at the apical side of human BBB, and RAGE is also involved in sA ▪ 1-40 transcytosis [94].

It has been shown that the interaction between Aβ/RAGE in the luminal membrane of the BBB participates in; 1). The diffusing of Aβ from the circulation to the brain through the BBB parenchyma, 2) Endothelial NF-KB mediated activation resulting in the secretion of pro-inflammatory cytokines (TNF-α and IL-6) and adhesion molecules expression (ICAM-1 and VCAM) and 3), generation of endothelin-1 decreases cerebral blood flow (CBF). The peptide Aβ / RAGE interaction contributes directly to neuronal death producing oxidative damage to neurons expressing RAGE and indirectly through activation of microglia [95]. Inhibition of RAGE/Aβ interaction in affected vasculature inhibits the production of cytokines, oxidative stress and Aβ peptide transport across the BBB [96]. Therefore it is suggested that RAGE could be an excellent therapeutic target in AD. It has been shown that RAGE inhibitors block its interaction to Aβ peptide and stabilizes the BBB functions, reducing neuroinflammation and improving the CBF.

14. Alterations of the neurovascular unit in AD

As previously described Aβ aggregates activate microglia and astrocytes, promoting the secretion of cytotoxic and pro-inflammatory factors culminating in neuronal and BBB dys-function. Aβ can accumulate in the cerebral blood vessels, causing a morphofunctional alteration of neurovascular function.

Human brain receives 20% of the total cardiac output, if the cerebral blood flow (CBF) is stopped, so do brain functions in seconds and damage to neurons occurs in minutes [97]. The neuron-vessel relationship is critical for normal brain function. It has been estimated that each neuron in the human brain has its own capillary [98].

The length of brain capillaries is reduced in AD. These reductions can decrease vascular transport of substrates and nutrients through the BBB and reduce disposal of neurotoxins [99]. Vascular cells can directly affect the synaptic and neuronal functions through alterations in blood flow, the permeability of the BBB, nutrient supply, removal of toxic molecules, enzy-matic functions, secretion of trophic factors and matrix molecules or through abnormal

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expression of vascular receptors [100]. In response to vascular injury, astrocites and microglia are recruited, which when activated secrete several pro-inflammatory cytokines [101], that in turn, damage and exacerbates neuronal and synaptic dysfunction.

15. Stages of neurovascular dysfunction in AD

In early stages of AD, Aβ peptide removal through the BBB is impair, which could favour the accumulation of neurotoxic Aβ oligomers in the brain. Moreover, Aβ oligomers and focal reduction in capillary blood flow may affect synaptic transmission, causing neuronal damage and initiate the recruitment of microglial cells or blood within the brain [100].

In the early AD symptomatic stage, the BBB start missing Aβ removal properties, and activated endothelium and pro-inflammatory cytokines secreted to the CBF. This increases synaptic dysfunction, accumulation of intracellular tangles and activation of microglia. In late symptomatic AD stages, capillary unit is impair and contribute to the degeneration of the endothelial barrier. At this stage, there is a severe loss of the ability of the BBB to remove Aβ, resulting in amyloid deposits formation in the outer side of the capillary membrane, an increase in the number of NFT and activated microglia and astrocytes. At the final AD stages, the capillary unit is lost due to the amyloid deposits, therefore altering neuronal synapsis (Figure 6) [100].

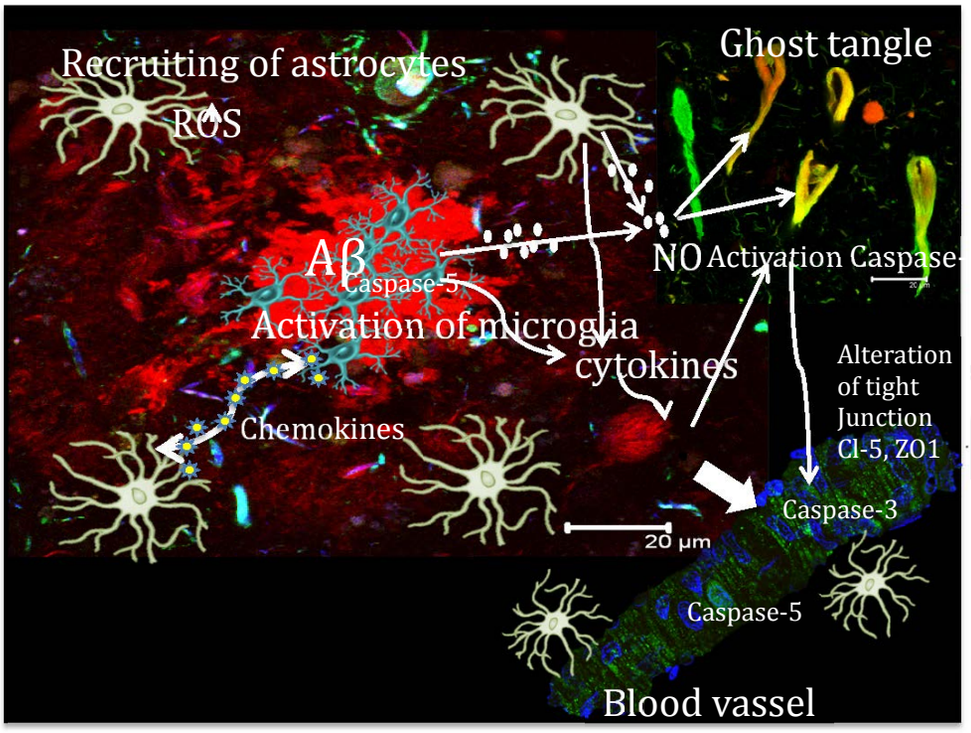


Figure 5. Schematic representation of neuroinflammatory environment and BBB alterations in AD. Aβ aggregates activate microglia and astrocytes, which will secrete pro-inflammatory cytokines and cytotoxic factors that will cause neuronal damage and disruption of the BBB (See more details in text).

16. Brain microvascular dysfunction as early event in AD

It is proposed that the breakdown of the BBB might be directly responsible for the pathogenesis of sporadic AD or at least could participate synergistically with other pathogenic mechanisms in the development of dementia [102]. Altering the BBB might occur as a result of hypoxia and complication of ischemic events, causing myocardial alterations commonly observed in AD. The breakdown of the BBB in AD is supported by the anatomical thickness and functional changes in the cerebral microvasculature [102] Deposits of A ▪ in the cerebral vasculature, leading to thickening of the basement membrane, stenosis of the vessel lumen and fragmentation of the internal elastic lamina, which can lead to stroke, brain haemorrhage or dementia [103, 104].

In AD there are ultrastructural changes [105] in the capillaries and changes in the its distribution and density [106]. It is believed that the accumulation of Aβ is one of the earliest events causing cerebrovascular alterations [107]. It has been detected changes in microvascular permeability and BBB dysfunction in AD brains [108]. BBB regulates the input of plasma derived Aβ and eliminates CNS Aβ through RAGE and the low-density lipoprotein receptor-related protein, (LRP1) respectively [95, 109].

The soluble peptide Aβ (s- Aβ) is normally produced by different cell types [110] and could be released into the circulation of the cerebrospinal fluid (CSF)[9] and brain parenchyma [111]. The Aβ 1-40 peptide represents about 90% of the total cerebrovascular amyloid [112]. High levels of Aβ and the presence of predisposing factors such as apoE4, genetic mutations in PS-1, PS-2 and APP [113], may favor the accumulation of Aβ as fibrillar amyloid in the wall vessel or in the brain parenchyma and could induce cytotoxic effects [95, 114] and contribute to neuronal loss and the development of the AD pathology [113].

Recent studies support the vascular theory to show that the brain distribution of Aβ receptors in the apical side of the BBB might be responsible for the interaction of Aβ circulating with the vascular wall and mediate its transit to the brain [115]. In AD many Aβ deposits are associated with microvessels [116] and with the presence of multiple inflammatory molecules that provide support for monocyte transmigration ability to neighbourhoods of Aβ deposit and in accordance with the clinical- pathological it has been suggested that neuroinflammation plays a role in patients with AD dementia [117]. In a study it was shown that Aβ peptide induced monocyte differentiation into macrophages and hypersecretion of inflammatory cytokines and chemokines [70]. In AD brains, a large number of core amyloid deposits in NPs are intimately associated with endothelial basal lamina and in many instances the lumen is lost [116]. It has also been found that calcium influx is induced by intracellular Aβ [118, 119], and that elevation of intracellular calcium leads to alteration of the TJ as the induction of MMPs [120].

Chronic transmigration of monocytes may result in subtle damage to the BBB. Disruption of the BBB would allow the passage of large amounts of circulating Aβ linked to other carrier proteins such as albumin [121], α-2 macroglobulin [53] and Aβ components. Albumin levels in CSF of patients with early stages of AD, found to be significantly enhanced due to an increased permeability of the BBB [122]. Elevated levels of other proteins of high molecular weight as haptoglobin, had also been found in this conditions [123].

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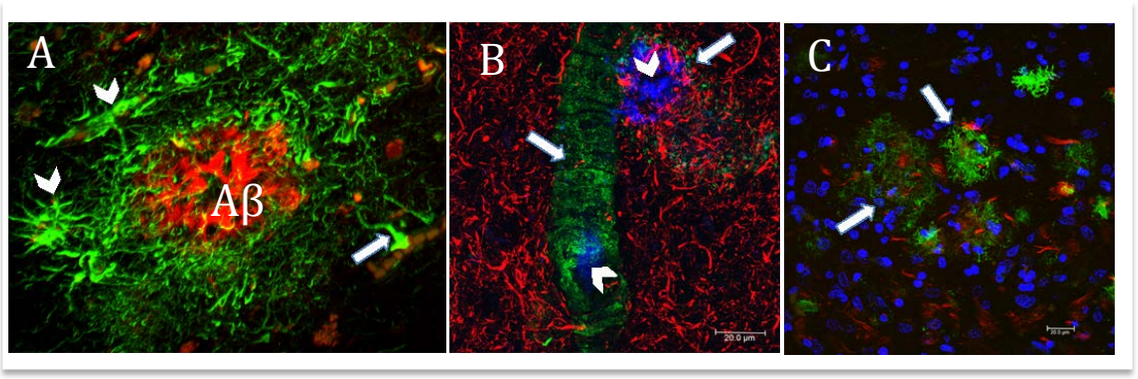


Figure 6. The extracellular deposits of amyloid-β peptide induces cronic inflammation in neuronal cell. A) Double immunostaining. Glial cell immunostaining evidenced by GFAP antibody (arrowheads), which is located in the perifery of the extracellular amyloid deposit evidenced by the thiazine red dye (Aβ). Microglial cell associated with a blood vessel. B) Triple immunostaining, where expression of caspase-5 (green channel) was detected in the cytoplasm of endothelial cells (the blood vessel, arrow). Adjacent to the blood vessel is possible to observed a extracellular Aβ deposit (amyloid plaque) evidenced by antibody BAM10 (arrowheads). In the red channel is the immunoreactivity of an antibody against tau protein. C) Double immunostaining with antibodies raised to Caspase-5 (green channel, arrows), which is strongly associated with amyloid plaques (as evidenced by the thiazine red staining, red channel), counterstained with Topro dye to show cell nuclei (blue channel). confocal microscopy, Leica SP8.

17. Amyloid beta peptide and intracellular caspase 5 in brain endothelial cells

Caspase-5 is expressed in a restricted manner in placenta, lung, liver, spleen, small intestine, colon and peripheral blood lymphocytes (1, 3) and it is located in the cell cytoplasm. It belongs to the family of proteins involved in apoptosis, inflammation, proliferation and differentiation. Caspase-5 operatively was associated with the caspases 1, 4 and 12.

Caspase-5 is regulated by lipopolysaccharide (LPS) and interferon-γ. Suggesting that caspase-5 may perform functions in inflammation and innate immune response. Likewise, it is associated with the complex of proteins that constitute the inflammasome. Caspase-5 also participates in IL-1β processing However the presence of caspase-5 and its role in neurodegenerative diseases is unknown.

In this review we have discuss the inflammatory role that is present in AD brains in response to Aβ accumulation and stress induced by this peptide, triggering a response in microglial and astroglial cells. Which are responsible for this inflammatory damage in AD. This proinflammatory cascade generated by microglial activation resulting from the release of cytotoxic molecules such as interleukins (IL-1 α, IL-1 β, IL-6, IL-10, IL-12, IL-16, IL-23), growth factors (transforming growth factor beta [TGF-β]), chemokines, matrix metalloproteinases (MMP-2, MMP-3, MMP-9), eicosanoids (PGD 2, leukotriene C4, cathepsins B and L) and complement factors (C1, C3, C4) also causing astrocytic chemotaxis around NPs (53). Activated microglia also releases excessive amounts of glutamate excitotoxicity, thereby inducing neurodegeneration. So far caspase-5 has been involved in Aβ induced neuroinflammation in AD brains. In

our laboratory we have detect the presence of caspase-5 closely associated with Aβ deposits in blood vessels (Fig. 6 B arrows) and Aβ plaques (Fig. 6 B. arrowhead, Fig. 6. C arrows) in AD brains. NPs showed a high immunoreactivity to caspase-5. The presence of caspase-5 was observed in the area where active microglial cells are and poorly observed in the periphery of the NPs where the astroglial cells are (Fig. 6). This does suggest that microglial cells carry out active inflammatory activity and are responsible for the neurotoxic environment observed in AD.

A large numbers of studies have demonstrated an increase of endothelial cells activity in blood vessels. By double and triple immunostaining and confocal microscopy, we have demonstrated the presence of soluble Aβ and fibrillar Aβ (evidenced by the monoclonal antibody BAM10 and stained with thiazine red (TR), which is used to monitor the fibrillar state of tau and Aβ peptide, with a β pleated sheet conformation.) in endothelial cell soma. It is possible that the accumulation of extracellular Aβ peptide could be trigger by caspase-5 activity, causing an increase in the synthesis of IL, therefore modifying the permeability of cerebral blood vessels by altering tight junctions in AD brains. Consequently the presence and activity of caspase-5 could promote the prolonged and sustained inflammation described in AD brains.

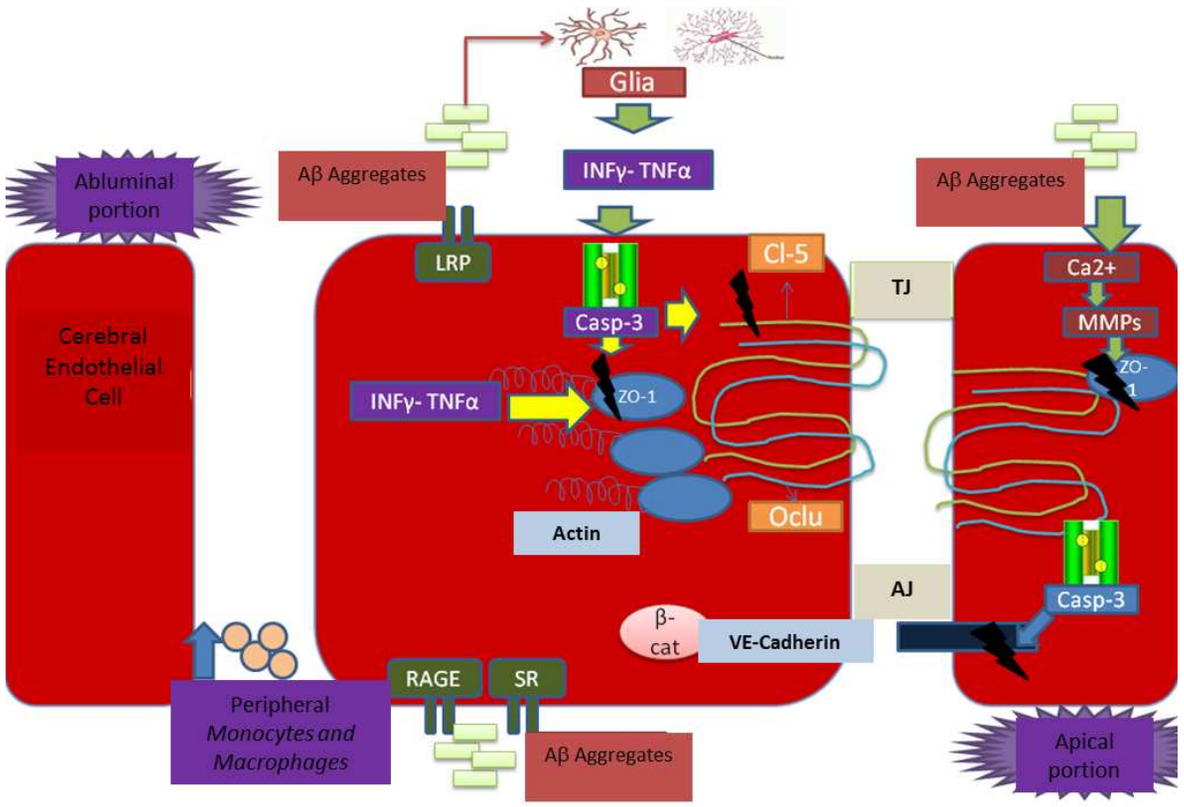


Figure 7. Disruption of the BBB in AD. Aβ aggregates activated glia, pro-inflammatory cytokines secretion, which in turn activate caspase 3, contributing to the disassembly of constitutive adherent junction proteins. The Aβ aggregates also contribute to activation of MMPs. BBB damage, allows monocytes, macrophages and peripheral Aβ aggregated to pass from outside the nervous system to the brain, increasing the neuroinflammatory environment.

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18. Conclusions

Amyloid β peptide, which is aggregated extracellularly in the neuritic plaques, generates a constant inflammatory environment and prolonged, activation of microglial and astroglial cells that potentiate neuronal damage and have been involved in the alteration of the BBB, damaging the permeability of blood vessels. Maybe as a consequence of degradation of tight junctions proteins, favouring the loss of these junctions, altering the permeability of blood vessels. Understanding the mechanisms of action of different species of beta amyloid peptide could lead to new therapeutic interventions directed to inhibit Aβ aggregation at the level of oligomers, which are much more toxic than the fibrillary form. It is important to understand the mechanisms of action of caspase-5, in this pathological process of amyloid β peptide, emphasizing the clinical importance of casapasa-5 and its relation to the process of neuroinflammation.

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