



Pathological alteration in the choroid plexus of Alzheimer's disease: implication for new therapy approaches

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Morphological alterations of choroid plexus in Alzheimer's disease (AD) have been extensively investigated. These changes include epithelial atrophy, thickening of the basement membrane, and stroma fibrosis. As a result, synthesis, secretory, and transportation functions are significantly altered resulting in decreased cerebrospinal fluid (CSF) turnover. Recent studies discuss the potential impacts of these changes, including the possibility of reduced resistance to stress insults and slow clearance of toxic compounds from CSF with specific reference to the amyloid peptide. Here, we review new evidences for AD-related changes in the choroid plexus. The data suggest that the significantly altered functions of the choroid plexus contribute to the multiparametric pathogenesis of late-onset AD.

Keywords: choroid plexus, Alzheimer's disease, amyloid, mitochondria, cell death, oxidative stress

INTRODUCTION

In the recent years, much attention has been directed to the roles of the choroid plexus in the central nervous system (CNS) under both normal and pathological conditions. This specialized ventricular structure has recently emerged as a key player in a variety of processes that monitor and maintain the biochemical and cellular homeostasis of the CNS.

The main role of the choroid plexus is to produce cerebrospinal fluid (CSF) and to maintain the extracellular environment of the brain by monitoring the chemical exchange between the CSF and the brain tissue. This involves the surveying of the chemical and immunological status of the extracellular fluid and the removal of toxic substances as well as important roles in the regenerative processes following traumatic events. In addition to CSF, the plexus produces various peptides which can have nourishing and neuroprotective properties.

The choroid plexus is subject to various external factors and undergoes structural and physiological changes during aging and disease states. Detrimental changes in the choroid plexus anatomy, function, and CSF turnover have been found in several neurological diseases, including Alzheimer's disease (AD; Serot et al., 1997, 2000, 2003; Preston, 2001; Stopa et al., 2001; Emerich et al., 2004; Alvira-Botero and Carro, 2010). In the present review we present and summarize the recent findings on pathogenic processes occurring within the choroid plexus and discuss their direct and indirect effects on the mechanisms of AD.

CHOROID PLEXUS IN AD PATIENTS

Alzheimer's disease is characterized by the production and accumulation of β -amyloid (A β) species in the form of oligomers, fibrils, and large aggregates called A β deposits leading to classical senile plaques in the brain, and vascular deposits (amyloid angiopathy) in brain and meningeal blood vessels (Gentile et al., 2004). Recent advances have led to a better understanding of the cellular and molecular pathways of AD. Although amyloid cascade

theory as the primary cause of the disease is actually a controversy, pathological mechanisms in this cascade involve neurotoxic effects of amyloid peptides probably producing oxidative damage and apoptosis in brain cells, including choroid plexus epithelial cells (Perez-Gracia et al., 2009; Vargas et al., 2010b). However, there are alternative proposed processes or hypotheses which might be involved in pathological development of AD.

Recently, emphasis has focused on comorbidity of AD and the deficient clearance of A β across the blood-brain barrier (BBB; Deane et al., 2004; Tanzi et al., 2004; Zlokovic, 2004) and the blood-CSF barrier (BCSFB; Zlokovic et al., 1996). The traditional role ascribed to the choroid plexus has been to provide physical protection to the brain and to facilitate removal of brain metabolites through bulk drainage of CSF. However, recent studies suggest that the choroid plexus-CSF system plays a much more active role in AD (Weller, 1998; Stopa et al., 2001; Carro et al., 2006; Maurizi, 2010; Vargas et al., 2010b).

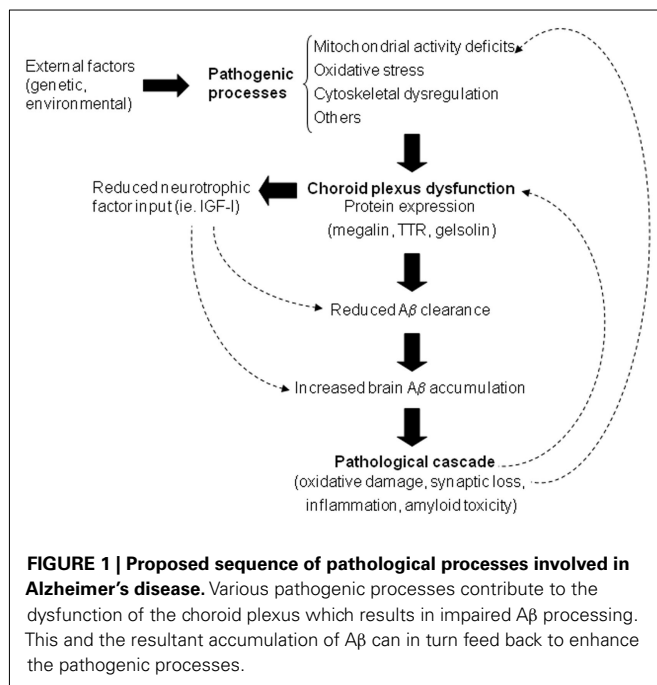
The choroid plexus is subject to morphological and physiological changes that produce a wide range of effects. In AD the choroid plexus develops abnormalities similar to those observed with aging, although greatly enhanced. Epithelial atrophy is significantly accentuated: a decrease in cell height is observed compared to age-matched controls (Serot et al., 2000). Epithelial cells acquire numerous lipofuscin vacuoles and Biondi bodies increase significantly in AD patients (Miklossy et al., 1998; Wen et al., 1999; Alvira-Botero and Carro, 2010). These modifications could alter choroid plexus functions, including synthesis, secretion, and transport of proteins and other molecules. Although this is not enough to cause amyloid deposits in the majority of AD cases, the authors consider the condition of the choroid plexus an important factor in the initiation and development of AD pathology. Moreover, the authors hypothesize that disrupted choroid plexus functions may precede several AD hallmarks, including amyloid brain accumulation. In the authors' view, altered choroid plexus functions may be, at least, one of the primary pathogenic events in late-onset AD

(**Figure 1**). Multifactorial changes, including genetic and environmental alterations, result in a number of common mechanisms of degeneration, such as mitochondrial dysfunction, oxidative stress, calcium homeostasis dysregulation, and a global decrease of functional choroid plexus.

A β DEPOSITS

The appearance of neurofibrillary tangles and extracellular senile plaque deposition, whose major constituent is A β , are the main hallmarks of AD (Selkoe, 2000a,b). Besides accumulating in brain parenchyma and blood vessels, A β also accumulates in choroid plexus (Dietrich et al., 2008). Several data have shown pathological argyrophilic filaments with histochemical properties of amyloid showing striking morphological similarity to curly fibers and/or tangles accumulating in epithelial cells of choroid plexus (Reusche, 1997; Miklossy et al., 1998, 1999; Wen et al., 1999). Recent results from our group revealed the presence of A β deposits in the choroid plexus in autopsy material from AD patients, and suggest a direct relationship between A β deposits at choroid plexus epithelium and the development of a functional and structural disruption of the organ (Dietrich et al., 2008).

Soluble A β , a product of the secretory pathway in amyloid precursor protein (APP) processing, is produced by the choroid plexus as observed in both rat and human post-mortem tissue (Kalaria et al., 1996). APP is synthesized also by many cells outside the CNS and deposition of A β protein was reported to occur in non-neuronal tissues (Biewend et al., 2006). As shown in **Figure 2**, A β immunoreactivity is detected in choroid plexus epithelial cells from non-demented subjects, but the proportion of epithelial cells containing A β accumulation increases significantly in choroid plexus from AD patients (**Figure 2**). The authors suggest that A β probably accumulates in the choroid plexus secondary to a dysfunction and a pathological cascade as illustrated in **Figure 1**.



The deficits in mitochondrial activity, increase in oxidative stress together with above mentioned morphological changes which are observed in AD, are likely to lead not only to abnormal brain A β clearance at the BCSFB, but also increased or defective A β processing from APP, which has been described in choroid plexus (Kalaria et al., 1996; Premkumar and Kalaria, 1996) and would contribute to the development of A β accumulation in this tissue.

MITOCHONDRIAL ACTIVITY

Mitochondrial dysfunction is one of the earliest deficits identified in AD brains (Valla et al., 2001; Beal, 2005; Manczak et al., 2006). It has been described that mitochondrial enzyme activity defects occur in hippocampal neurons and choroidal epithelial cells more frequently in AD patients (Cottrell et al., 2001). Increase in the number of COX-deficient choroid epithelial cells provides strong evidence that a substantial mitochondrial enzyme activity decline occurs in individual cells more frequently in AD than in normal aging. This deficiency in mitochondrial enzyme activity is likely to result in a decrease in transport across the epithelial cells and thus has implications in choroidal A β clearance, highlighting the role of mitochondria in the pathogenesis of AD.

On the other hand, several studies indicate that A β itself can impair mitochondrial function (Canevari et al., 1999; Casley et al., 2002a,b). Since A β deposits accumulate in the choroid plexus of AD patients (Dietrich et al., 2008), it is likely that A β interferes with their function. In a recent study, we have shown that mitochondrial dysfunction in choroid plexus from AD subjects occurs through a down-regulation of mitochondrial proteins and activity (Vargas et al., 2010b). In this study, the authors observed a decrease in cytochrome *c* oxidase activity in the choroid plexus of AD patients. The *in vitro* analysis carried out in choroid plexus epithelial cells revealed a reduction in the activity of respiratory chain complex I and IV directly caused by A β exposure (Vargas et al., 2010b).

OXIDATIVE STRESS AND CELL DEATH

Oxidative damage to proteins is a relative early phenomenon in the pathogenesis of AD. A number of oxidatively damaged proteins have been reported in the hippocampus and inferior parietal lobules of cases with mild cognitive impairment and AD-related pathology corresponding to Braak stages III, IV, and V (Butterfield et al., 2006; Reed et al., 2008). In the choroid plexus on the

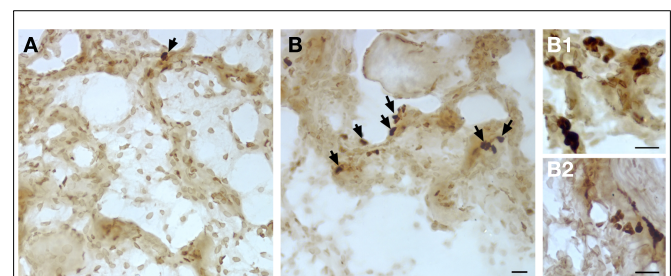


FIGURE 2 | A β deposits (arrows) detected in choroid plexus from AD patients. (A) Choroid plexus tissue from age-matched control patient; **(B)** Choroid plexus from an AD patient. **(B1,B2)** High magnification of the A β deposits from AD patients. Scale bar = 20 μ m, $n = 3$ per group, ≤ 10 fields observed from each sample.

other hand, oxidative protein damage occurs at later stages of AD than in other brain areas (Perez-Gracia et al., 2009). The proteins affected by oxidation in the choroid plexus were found to be 14-3-3, tropomyosin, and apolipoprotein A-II. Such oxidation may result in impaired protein interactions, protein folding and protein kinase activity, abnormal function of endothelial and vascular smooth muscle cells, and impaired HDL cholesterol metabolism, thus having important implications in the deterioration of the functions of the plexus (Perez-Gracia et al., 2009).

Abnormal patterns of stress protein expression are found in the cerebral cortex and hippocampus of AD subjects (Anthony et al., 2003). A decreased HO-1 immunoreactivity has been observed in the AD choroid plexus, in agreement with suppressed HO-1 protein levels in AD CSF (Schipper et al., 2000; Anthony et al., 2003). Heat shock protein (HSP) 90, a steroid receptor chaperone, was up-regulated in the AD choroid plexus relative to controls, and there was a trend toward an increased expression of HSP60, a mitochondrial stress protein. This is in agreement with mitochondrial pathology recently documented in AD choroid plexus (Cottrell et al., 2001; Vargas et al., 2010b).

In a recent study from our group, we have described an increased nitric oxide (NO) production by the choroid plexus of AD patients, associated with A β deposits (Vargas et al., 2010b). A similar situation was observed in the choroid plexus of 12-month-old APP/PS1 mice, which had a noticeably high A β expression. Excessive generation of NO has been implicated in the pathogenesis of AD (Smith et al., 1997; Aliyev et al., 2004), and plays an important role in A β -induced mitochondrial dysfunction (Keil et al., 2004). The interaction between NO and cytochrome *c* oxidase controls mitochondrial production of hydrogen peroxide, which has been shown to be implicated in cellular redox signaling (Galli et al., 2003; Carreras et al., 2004). These results, together with previous findings (Veereshwarayya et al., 2006; Petrosillo et al., 2007), support the hypothesis that A β interferes with oxidative phosphorylation, which results in oxidative stress, and demonstrate that reactive oxygen species (ROS) generation is secondary to mitochondrial damage.

The authors also suggest that A β is involved in cell death pathway in choroid plexus since results from our group showed that A β -treated choroid plexus epithelial cells have an increased expression of caspases 3 and 9 (Vargas et al., 2010b). This finding is consistent with another study, where APP transfected cells showed a significant increase in the expression and activity of caspases 3 and 9 (Marques et al., 2003). These data suggest that the excessive generation of ROS would be responsible for initiating the apoptotic cell death process by up-regulating caspase signaling, as previously demonstrated (Takuma et al., 2005; Zhu et al., 2006).

PROTEIN EXPRESSION, SYNTHESIS, AND SECRETION

The structure and location of the choroid plexus allows it for the distribution of molecules throughout the CSF and to the brain parenchyma as well as locally. This ventricular structure possesses

a multitude of specific transporters and receptors and many biologically active compounds are produced at the choroid plexus, including a large number of neuropeptides, growth factors, and cytokines (Stopa et al., 2001; Alvira-Botero and Carro, 2010). The above characteristics allow the plexus to exert a fine control over the CNS extracellular fluid, responding to changes, and maintaining baseline levels (Stopa et al., 2001).

Within the list of choroid plexus related proteins, the expression of a vast range of them is significantly diminished in AD, including vascular endothelial growth factor (VEGF; Spuch et al., 2010), transthyretin (Sousa et al., 2007; Dietrich et al., 2008), gelsolin (Vargas et al., 2010a), apolipoprotein J (Carro et al., 2006). TTR, gelsolin and ApoJ bind brain A β , and are involved in its clearance via the endocytotic receptor megalin (Zlokovic et al., 1996; Chauhan et al., 1999; Carro et al., 2002; Antequera et al., 2009). It has also been observed that megalin expression is reduced in the choroid plexus in APP/Ps1 mice and AD patients (Dietrich et al., 2008). We suggest that A β accumulation in the choroid plexus could disturb megalin-mediated transport and protein synthesis.

As previously reported, the choroid plexus regulates the transport of many growth factors, including brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), VEGF, insulin, and insulin-like growth factor (IGF-I). In the case of IGF-I, megalin is involved in IGF-I transport from blood into the brain, and a decrease in megalin would result in low IGF-I input to the brain (Carro et al., 2005). As a consequence, the potential protective roles of IGF-I in AD would be compromised, including modulation of A β clearance, brain amyloid content, and neuroprotection against A β toxicity (Carro and Torres-Aleman, 2004).

CONCLUSION

In this review we have proposed that choroid plexus dysfunction can be a major contributing factor to the pathology of AD. Pathogenic processes such as mitochondrial activity deficits, oxidative stress, and morphological structural changes contribute to the decreased efficacy of the choroid plexus in clearing of A β , thus resulting in an A β accumulation in the brain. This in turn induces further pathological cascades of toxicity, inflammation, and neurodegeneration and may feedback to further enhance the disease process.

To date, the therapeutic targets have focused on diminishing the A β burden. However, we propose that targeting the upstream events such as mitochondrial deficits and oxidative stress as well as the choroid plexus carrier proteins (megalin, gelsolin) may prove to be more effective. Also, given that the choroid plexus itself has the ability to produce a nutritive "cocktail" of neurotrophic factors, there is evidence indicating that transplanted choroid plexus epithelial cells may potentially be used to protect neurons from excitotoxic damage (Emerich et al., 2004, 2005; Borlongan et al., 2008; Thanos et al., 2010).

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