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Oligodendrocytes damage in Alzheimer's disease: Beta amyloid toxicity and inflammation

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ABSTRACT

Research on Alzheimer's disease (AD) focuses mainly on neuronal death and synaptic impairment induced by β-Amyloid peptide (Aβ), events at least partially mediated by astrocyte and microglia activation. However, substantial white matter damage and its consequences on brain function warrant the study of oligodendrocytes participation in the pathogenesis and progression of AD. Here, we analyze reports on oligodendrocytes' compromise in AD and discuss some experimental data indicative of Aβ toxicity in culture. We observed that 1 μM of fibrilogenic Aβ peptide damages oligodendrocytes *in vitro*; while pro-inflammatory molecules (1 μg/ml LPS + 1 ng/ml IFNγ) or the presence of astrocytes reduced the Aβ-induced damage. This agrees with our previous results showing an astrocyte-mediated protective effect over Aβ-induced damage on hippocampal cells and modulation of the activation of microglial cells in culture. Oligodendrocytes protection by astrocytes could be, either by reduction of Aβ fibrilogenesis/deposition or prevention of oxidative damage. Likewise, the decrease of Aβ-induced damage by proinflammatory molecules could reflect the production of trophic factors by activated oligodendrocytes and/or a metabolic activation as observed during myelination. Considering the association of inflammation with neurodegenerative diseases, oligodendrocytes impairment in AD patients could potentiate cell damage under pathological conditions.

Key terms: cell death, glial cells, pro-inflammatory cytokines.

One of the major histopathological characteristics of Alzheimer's disease (AD) is the presence of senile plaques (SP), composed mainly of Amyloid β peptide (Aβ) aggregates and activated microglia at the center, surrounded by a crown of activated astrocytes. Glial activation results in the sustained production of pro-inflammatory molecules, giving rise to a chronic inflammatory process. Research on AD has focused mostly on the generation of Aβ peptide and its induction of neuronal damage (see review by Selkoe, 2004; Cerpa et al., 2003; Lorenzo, 2004), while the importance of astrocyte and microglial activation induced by Aβ has gained recognition in the last few years (von Bernhardi and Ramírez, 2001; von Bernhardi and Eugenín, 2004). However, although oligodendrocytes (OLGs) are in intimate contact and are key for the morphofunctional maintenance of neurons, there is little information about Aβ cytotoxicity on OLGs.

WHITE MATTER DAMAGE AND OLIGODENDROCYTES PATHOLOGY IN ALZHEIMER'S DISEASE

The presence of white matter lesions (WML) and myelin abnormalities in the brain of AD patients is well supported by cytopathological (Braak et al., 2000; de la Monte, 1989; Englund et al., 1988; Kobayashi et al., 2002), neurochemical (Malone and Szoke, 1985; Roher et al., 2002; Sevennerholm and Gottfries, 1994),

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electrophysiological (Tanaka et al., 1994) and live imaging techniques (Bartzokis et al., 2003, 2004; de Leeuw et al., 2004). While WML are a hallmark of cerebrovascular pathology, evidence suggest that they are also related to AD (Brown et al., 2000; Vermeer et al., 2003; Decarli, 2004), particularly, the correlation between WML and hippocampal atrophy in AD patients (de Leeuw et al., 2004) and their effect on cognition decay (Decarli, 2004), which could reflect Aβ deposition around blood vessel walls and subsequent ischemia (Iwatsubo et al., 1994), a situation to which OLGs are particularly vulnerable (review by Volpe, 1998). Whereas it is still unknown whether OLG damage is part of the AD pathogenesis or a consequence of other pathological processes, it has been proposed that differences in myelination onset (Braak and Braak, 1996; Power et al., 2002) can increase the susceptibility for myelin breakdown and subsequent axonal dysfunction, a process observed during aging (Nielsen and Peters, 2000) and exacerbated in AD (Bartzokis et al., 2004). A decrease of OLGs would have a profound effect on neuronal function and viability, since OLGs provide trophic and metabolic support for neurons and axons (Du and Dreyfuss, 2002; Dai et al., 2003; Court and Alvarez, 2005).

An unsolved point is whether myelin loss would be secondary to neuronal death and the subsequent axonal degeneration, resulting in the white matter patterns detected by imaging (Noble, 2004). While myelin damage can result from axonal degeneration, it also is induced by several insults (Bartzokis, 2004), including Aβ (Curtain et al., 2001; Kiuru et al., 1999) and radical oxygen species (ROS) (Whitman and Cotman, 2004). Myelin abnormalities described in AD are observed in the absence of evident of axonal damage (Umahara et al., 2002; Bartzokis et al., 2003) and are similar to the defects in the formation of myelin sheaths observed in aging individuals (Nielsen and Peters, 2000). The neurons first affected by AD are those that are myelinated at the latest periods of life (Braak and Braak, 1996). It has been suggested that the death of myelinating OLGs would be a critical initiating step of AD (Bartzokis et al., 2004).

OLIGODENDROCYTES DEATH INDUCED BY AB

High levels of Aβ are observed in the white matter of AD patients (Roher et al., 2002; Wiesniewski et al., 1989), and as mentioned above, Aβ aggregates are considered responsible for the neuronal and vascular degeneration in AD brains (Yankner et al., 1989; Thomas et al., 1996). Although the molecular mechanism of Aβ-mediated cell death is not clearly defined, it is known that it probably involves oxidative stress, a situation to which OLGs are particularly susceptible because their reduced glutathione (GSH) content is low and they have a high concentration of iron, thus presenting an impaired ability to scavenge oxygen radicals (Back et al., 1998; Juurlink et al., 1998). Furthermore, Aβ possesses an increased capability for damaging cholesterol rich membranes, such as those found in OLGs and myelin (Subasinghe et al., 2003).

Aβ toxicity on OLGs has been assayed using the Aβ fragments that span amino acids 1 through 40 ($A\beta_{1-40}$) or 25 through 35 ($A\beta_{25-35}$), but there are no reports using the full and most amyloidogenic Aβ peptide ($A\beta_{1-42}$). Aβ-induced OLG death presents characteristic features of apoptosis (Xu et al., 2001), mediated through the activation of the nSMase-ceramide cascade (Lee et al., 2004). It possibly involves TNFα, neurotrophin receptor p75, and Fas ligand and causes mitochondrial dysfunction and oxidative stress *in vitro* (Xu et al., 1998) and *in vivo* after stereotaxic injection of Aβ (Jantaratnotai et al., 2003). $A\beta_{1-40}$ and $A\beta_{25-35}$ are cytotoxic to oligodendrocytes expressing intermediate differentiation markers (Xu et al., 2001), and $A\beta_{25-35}$ toxicity has been assayed on mature OLGs (Lee et al., 2004). Maximal cytotoxic effects were observed at peptide concentrations above 20 μM.

We studied the cytotoxicity of $A\beta_{1-42}$ on OLGs obtained from neonatal rat brain cultures that exhibited the characteristic

morphology of the oligodendroglial cell linage, large cell bodies with multiple branching processes and lamellipodia (Fig 1A) and expressed OLGs-specific markers galactocerebroside (GalC), cyclic nucleotide 3'-phosphodiesterase (CNPase), and the OLG mature state marker: Myelin Basic Protein (MBP, Fig 1A). Exposure of OLG cell cultures to 1 μM of $A\beta_{1-42}$ induced: cell death, as evidenced by a 40% decrease of MTT reduction activity (MTT, Fig 1B); morphological changes suggestive of damage, such as the breakdown of OLGs processes and appearance of shrunken cell bodies (Fig 2A); and an 3.2-fold increase of lactate dehydrogenase activity released to the culture media (LDH; Fig 2B). The $A\beta_{1-42}$ concentrations used were 10 to 30 times lower than those reported for $A\beta_{1-40}$ and $A\beta_{25-35}$ (Xu et al., 2001; Lee et al., 2004). This higher toxicity could reflect a higher sensitivity of mature oligodendrocytes to Aβ, compared to that of immature cells, or alternatively it could depend at least partially on the stronger amyloidogenic and fibrilogenic properties of $A\beta_{1-42}$ (Riek et al., 2001), which we used in these experiments.

OLG damage by $A\beta_{1-42}$ was decreased in cultures containing astrocytes (Fig 1B). This preservation of the MTT reduction could result through the lowering of $A\beta_{1-42}$ damage effectors, such as ROS, in agreement with the high level of antioxidants (Wilson, 1997) and detoxification enzymes present in astrocytes (reviewed by Minn et al., 1991).

In OLGs exposed simultaneously to $A\beta_{1-42}$ and proinflammatory molecules (LI), cell death was reduced by nearly 50%, although it remained significantly higher than that observed under control conditions ($p=0.0038$). We have observed previously that proinflammatory molecules protect hippocampal neurons from $A\beta_{1-42}$ neurotoxicity (Ramírez et al., 2005), an effect that depended on the presence of astrocytes or its conditioned media (von Bernhardi and Eugenín, 2004; Ramírez et al., 2005), which appears to be mediated by TGFβ1 (Herrera-Molina and von Bernhardi, 2005; Ramírez et al., 2005). The OLG protection by LI was not dependent on the presence of astrocytes, but might result from OLGs ability to release trophic molecules when stimulated (Dai et al., 2003; Du and Dreyfuss, 2002). While our results contradict the mainstream notion that proinflammatory molecules necessarily contribute to the progression of myelin and OLG damage (Merrill et al., 1993; Smith et al., 1999; Xie et al., 2002; Popovic et al., 2002), we propose that low levels of inflammation may prime a subpopulation of cells, activating certain cell signaling pathways (Leyton and Quest, 2004) and modifying calcium homeostasis (Campanella et al., 2004), allowing them to resist a certain degree of injury. In that sense, whereas we cannot provide a definitive explanation, we propose that a factor that could explain the contradiction could be the maturity of our OLGs. It has been shown that low concentrations of TNFα alter differentiation rather than cell survival (Cammer, 2000), a situation which could allow OLGs to activate ROS damage-reducing systems, such as the increase of peroxisomal enzymes during myelination (Lazo et al., 1991). Our results also suggest that an aggressive inhibition of glial inflammatory responses to Aβ may not result in decreased oligodendrocytes and neuronal damage as previously thought.

RECAPITULATION

1. Treatment of mature oligodendrocytes with 1 μM $A\beta_{1-42}$ resulted in mature OLGs death as measured by a decrease of MTT reduction and an increase of LDH release.

2. The cytotoxic effect of $A\beta_{1-42}$ on oligodendrocytes was prevented by co-culture with astrocytes and by the presence of pro-inflammatory molecules (LPS and IFN-γ), although regressive morphological changes suggesting damage persisted.

3. The functions served by oligodendrocytes suggest that, even if myelin damage on AD was secondary (e.g. to neuronal death), the loss of the trophic support they provide could lead to an increased vulnerability of neurons, increased inflammation, and further cell damage.

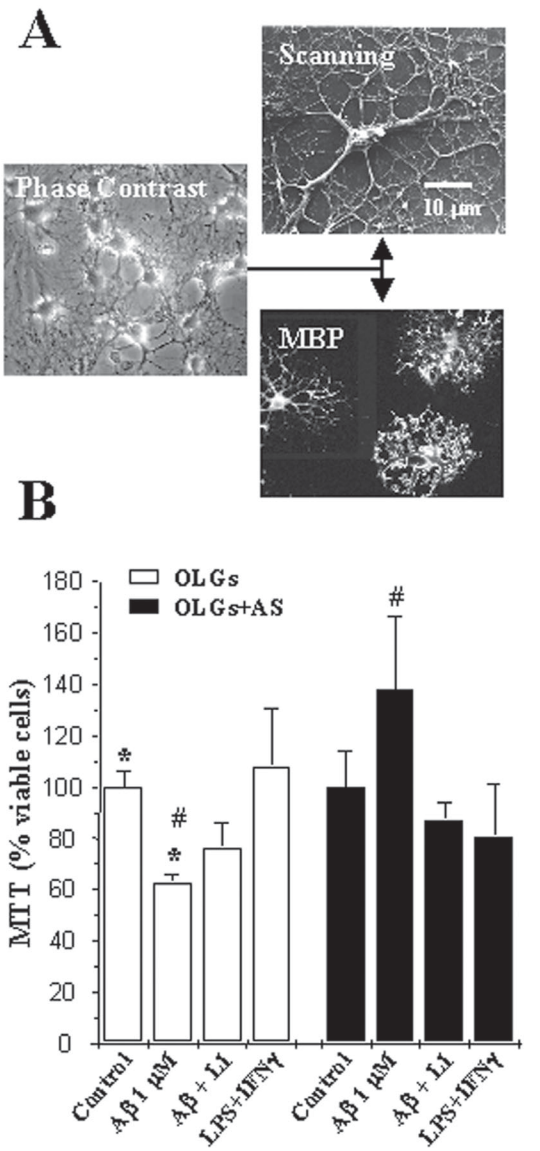

Figure 1. A. Characterization of mature differentiated oligodendrocytes. OLGs cultures were established according to McCarthy and de Vellis (1980), in the presence of chemically defined medium (without serum) as described by Nobel and Mayer-Pröschel (1998). Phase contrast and scanning electron microscopy of mature OLGs with characteristic branching cell processes. Immunocytocheminal labeling of OLGs cultures with an antibody against MBP (1/400 MAB386, Chemicon International) as marker for mature OLGs showing intense MBP immunoreactivity.
B. Cell viability measured by the MTT assay: Aβ decreases the reduction metabolism of OLGs. Reduction activity of oligodendrocytes (OLGs) and oligodendrocytes plus astrocytes (OLGs+AS). Cell cultures were treated with 1 µM Aβ (**Aβ**), 1 µg/ml LPS+ 10 ng/ml IFN-γ (**LI**), or Aβ + LI for 24 hr. Aβ decreased MTT reduction, but its effect was reduced when OLGs were co-cultured with astrocytes. Values correspond to the mean ± SEM from cell cultures exposed to 2 different preparations of fibrillar Aβ, in triplicate, with similar results. Differences in the percentage of apoptotic cells and reduction activity of OLGs cultures were evaluated with a Kruskal Wallis H-one-way ANOVA Test ($p=0.035$). Once significant differences in the variance analysis were established, the different conditions were evaluated with a Wilcoxon Rank Sum/Mann-Whitney U-Test. * shows significant differences ($p=0.0026$) between Aβ with respect to control cultures. # shows a significant difference ($p<0.008$) for the cultures exposed to Aβ with and without astrocytes.

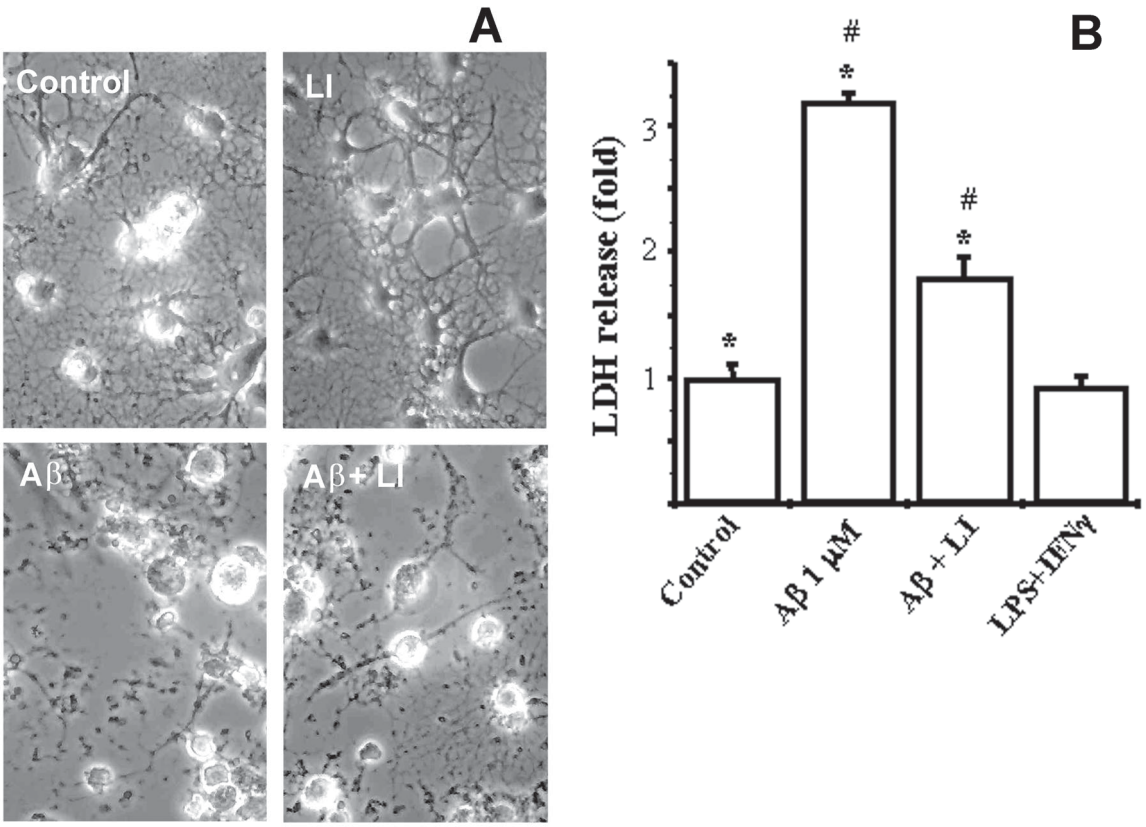

Figure 2. Morphological changes and cell death induced in OLGs by Aβ.
A. Phase contrast microscopy of OLGs cultures exposed to 1 μM of $A\beta_{1-42}$ (Aβ), 1 μg/ml LPS+10 ng/ml IFN-γ (LI) or LI+Aβ for 24 h. Note that, although cell death in cultures treated with LI+Aβ was reduced by 40% compared to OLGs exposed to Aβ (see panel B), profound morphological alterations remain. **B.** Cell death determined by the LDH assay in cultures exposed to the same conditions as in panel A. Results correspond to 3 independent OLGs cultures performed in triplicate. Error bars represent SEM. Differences in the LDH release were evaluated with a one-way ANOVA with a Kruskal Wallis H-Test ($p<0.001$). After determination of significant differences in the variance analysis, the different conditions were evaluated with a Wilcoxon Rank Sum/Mann-Whitney U-Test. * shows significant differences between cultures exposed to Aβ ($p<0.0001$) and to Aβ+LI ($p<0.0038$) with respect to control cultures. # shows significant differences between OLGs exposed to Aβ+LI ($p<0.0027$) with respect to those exposed to Aβ.

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