Published in final edited form as:
Alzheimers Dement. 2007 April ; 3(2): 122–125.

Human brain myelination and amyloid beta deposition in Alzheimer's disease

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Abstract

We hypothesized that myelin breakdown in vulnerable late-myelinating regions releases oligodendrocyte- and myelin-associated iron that promotes amyloid beta (Aβ) oligomerization, its associated toxicity, and the deposition of oligomerized Aβ and iron in neuritic plaques observed in Alzheimer's disease (AD). The model was tested by using published maps of cortical myelination from 1901 and recent in vivo imaging maps of Aβ deposits in humans. The data show that in AD, radiolabeled ligands detect Aβ deposition in a distribution that matches the map of late-myelinating regions. Furthermore, the strikingly lower ability of this imaging ligand to bind Aβ in animal models is consistent with the much lower levels of myelin and associated iron levels in rodents when compared with humans. The hypotheses derived from the "myelin model" are testable with current imaging methods and have important implications for therapeutic interventions that should be expanded to include novel targets such as oligodendrocytes, myelin, and brain iron.

Keywords

Myelin; Oligodendrocyte; White matter; Amyloid; Iron; Alzheimer's disease; PIB; Degeneration; Dementia; Aging; Medications; Treatment; Prevention

1. Introduction

The extensive scope of myelination is the single-most unique aspect in which the human brain differs from that of other species [1–3]. In this myelin model of human evolution and development, our brain's extensive myelination accounts for the high processing speeds and precise temporal coding underlying higher cognitive and behavioral functions [4,5]. Myelin and the oligodendrocytes that produce it are extremely vulnerable to a variety of insults including those caused by amyloid beta (Aβ) oligomers and fibrils [4,6,7]. The vulnerabilities of oligodendrocytes and myelin, especially later-developed myelin, are directly pertinent to many uniquely human degenerative disorders such as Alzheimer's disease (AD) [3,4,7] in which white matter damage has been directly associated with brain parenchyma Aβ load [6, 8].

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Myelination produces a continuum of increasingly vulnerable oligodendrocytes as later-differentiating oligodendrocytes that populate later-myelinating association regions ensheath increasing numbers of axons with smaller axon diameters [9,10]. Thus, during development, the myelination process produces a roughly bilaterally symmetrical continuum of oligodendrocyte vulnerability (Figure 1B, D) [3,7]. Under the influence of multiple risk factors such as age, apolipoprotein E genotype, and increasing Aβ and iron levels, these thinner myelin sheaths are differentially lost with age (27% to 45% reductions) in a pattern of bilaterally progressive myelin breakdown [4,7,11–13]. The myelin breakdown process thus recapitulates the developmental process of myelination in reverse [14] and is hypothesized to underlie the progressive, bilaterally symmetrical spread of the pathognomonic lesions of AD (neuritic plaques and neurofibrillary tangles) from late-myelinating regions toward earlier-myelinating regions [3,4] (Figure 1A, C). A similar process of developmental recapitulation has been described clinically as a progression of the cognitive, functional, and neurologic declines that accompany AD [15].

Oligodendrocytes and myelin have the highest levels of iron of any brain cells [16–19]. Several lines of circumstantial evidence support the possibility that brain iron levels might be a risk factor for age-related neurodegenerative diseases such as AD [20,21]. Post mortem and in vivo studies have established that brain iron levels increase with age [21–25], and iron levels are abnormally elevated in age-related neurodegenerative diseases, suggesting that increased iron levels might contribute to their age risk factor [3,4,26]. Men have higher brain iron levels than women [21], and men also have a younger age at onset of AD [27,28]. In large representative American populations after statistically controlling for the risk associated with the apolipoprotein E (*APOE*) genotype, men have a peak risk for AD onset that is 5 years younger than in women [29,30]. Thus, the peak probability of AD is reached 5 years earlier for men than women: age 78 and 83 years for *APOE* e4/e4, age 91 and 96 for *APOE* eX/eX, and age 92 and 97 for *APOE* e4/eX, respectively [29]. Furthermore, in patients with Down syndrome, who have an elevated risk for developing AD on a genetic basis, men develop AD at an earlier age than women [31]. In women with Down syndrome, an earlier menopause, which increases peripheral iron levels [32], is associated with earlier age at onset of AD [33,34].

2. Methods, Results, and Discussion

Recent in vivo methods of imaging Aβ deposits in humans by using Pittsburgh Compound-B (PIB) [35] (Figure 1A, C) are strikingly consistent with a myelin-based model of human brain development and degeneration [3,4]. The PIB data show that in AD, Aβ deposition is also observed predominantly in late-myelinating regions [35–37] (Figure 1A, C). We hypothesized that myelin breakdown in vulnerable late-myelinating regions (Figure 1B, D) releases oligodendrocyte- and myelin-associated iron [19,21,28,38,39], thus promoting Aβ oligomerization, its associated toxicity, and deposition of oligomerized Aβ and iron in neuritic plaques [7,28,40–43] (Figure 1A, C). This hypothesis has been supported in transgenic mouse models that demonstrated increased vulnerability of oligodendrocytes to toxicity [44], age-related white matter volume reductions [45], and age-related iron deposition in amyloid plaques [42]. Human studies have likewise confirmed age-related myelin breakdown that is exacerbated in healthy *APOE* e4 carriers and AD subjects [7,43] and age-related increases in brain iron [21] that are exacerbated in AD subjects [28].

The unique myelination of the human brain might also help explain the conundrum of why in vivo Aβ labels have high retention in human brain amyloid and very low retention in rodent amyloid [46,47]. Transgenic mouse models as well as human studies have demonstrated that a strong association exists between tissue iron and the production of senile plaques [28,40–42]. Myelin and oligodendrocytes have the highest iron content of brain tissues. The percentage of dry brain weight in humans accounted for by myelin is 30% higher than in rodents [48], and

it is thus not surprising that rodents have much lower levels of brain iron (up to an order of magnitude) than humans [24,49,50]. Iron levels increase with age in both species [21,23,24, 42,50]. These age-related increases might contribute to both the age-related increase in amyloid plaques observed in both species [14,41,42] and the correlation between tissue iron and amyloid deposit load observed in late-myelinating regions [14,42] that are most vulnerable to myelin breakdown and the release of iron [3,7,21,28,43].

The estimated 30% higher proportion of myelin in human versus rodent brain [48] is disproportionately higher in late-myelinating brain regions (Figure 1A to D). These regions contain predominantly thinly myelinated fibers with smaller axons and thus contain an increased proportion of myelin [9,43]. The age-related loss of myelin from primarily these thinly myelinated small axons (estimated at 10% per decade [13]) would take a disproportionate toll in late-myelinating regions and make much higher iron levels available for interaction with Aβ and deposition in amyloid plaques in these regions [41,42].

The histologic gold standard for labeling Aβ deposits in tissue is thioflavine-S [41], and PIB is a thioflavine derivative [46,47]. In animal models thioflavine-Aβ reactivity has been associated with the presence of metals in the deposits of Aβ [41,51]. We therefore suggest that the striking similarity between published maps of human in vivo Aβ labels and maps of later-myelinating cortical regions (Figure 1A to D) [35,36] supports the myelin model of AD [3,4, 7]. The myelin model and known species differences in myelination and iron levels might also explain the human/rodent differences in Aβ label retention, with high iron levels in humans acting as a necessary “scaffolding” for the PIB label to bind to the amyloid plaques [46,47] in which Aβ and iron colonize [41,42,52,53].

The hypotheses derived from the myelin model are eminently testable with currently available imaging methods and animal models. These hypotheses have important implications for therapeutic interventions that could include novel primary prevention measures focused on targets such as oligodendrocytes, myelin, and brain iron [7,20,21,28,54,55].

Acknowledgements

Part of this work was supported by NIA Alzheimer’s Disease Center Grant (AG16570), NIMH grant (MH 0266029), Research and Psychiatry Services of the Department of Veterans Affairs.

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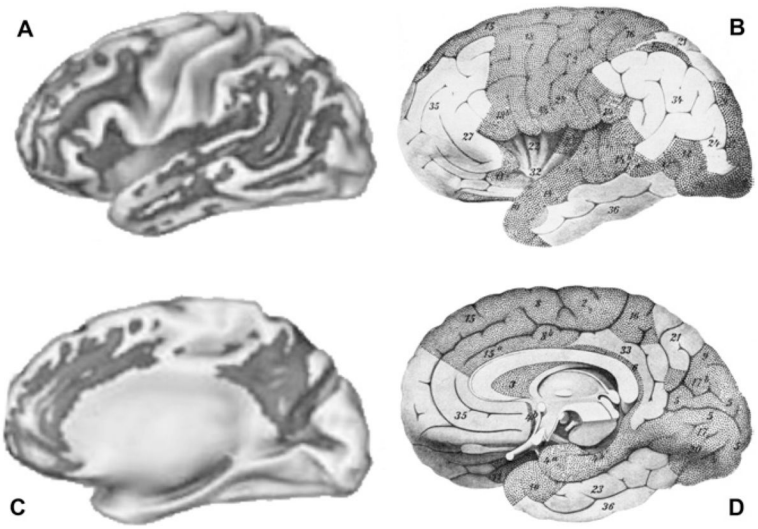

Fig 1.

(A) Amyloid deposition in dark grey, with lighter areas within the dark grey representing progressively more significant changes, as imaged with 11C Pittsburgh Compound-B, displayed in standard space lateral view. Reprinted from Buckner et al [35] with permission. Copyright 2005 by the Society for Neuroscience. (B) Late-myelinating regions in white; lateral brain view corresponds to positron emission tomography (PET)–derived image on the left. Reprinted from Meyer [37] with permission. (C) Amyloid deposition in dark grey, with lighter areas within the dark grey representing progressively more significant changes, as imaged with 11C Pittsburgh Compound-B, displayed in standard space medial view. Reprinted from Buckner et al [35] with permission. Copyright 2005 by the Society for Neuroscience. (D) Late-myelinating regions in white; medial brain view corresponds to PET-derived image on the left. Note: This image is “tilted” to expose the underside of the frontal and temporal lobe regions, which is not the case for the PET image on the left (C), and the exposed underside of those lobes should be ignored when comparing (C) and (D). Reprinted from Meyer [37] with permission.