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Jekyll and Hide

The two faces of amyloid β

Juliane Proft[1,*] and Norbert Weiss[2]

[1]Hotchkiss Brain Institute; Department of Clinical Neuroscience; Calgary, AB Canada; [2]Hotchkiss Brain Institute; Department of Physiology and Pharmacology; University of Calgary; Calgary, AB Canada

Neurodegenerative diseases are a burden of our century. Although significant efforts were made to find a cure or relief to this scourge, their pathophysiology remains vague and the cellular function of the key involved proteins is still unclear. However, in the case of amyloid β (Aβ), a key protein concerned in Alzheimer disease, we are now a step closer in the unscrambling of its cellular functions. Interestingly, whereas the exact role of Aβ in the pathophysiology of Alzheimer disease is still unresolved, a recent study revealed a neuroprotective function of Aβ in multiple sclerosis with possibly promising therapeutic benefits.

Keywords: multiple sclerosis (MS), amyloid beta (Aβ), T helper cells (TH), experimental autoimmune encephalomyelitis (EAE)

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Correspondence to: Juliane Proft;
Email: jproft@ucalgary.ca

Commentary to: JL Grant, EEB Ghosn, RC Axtell, K Herges, HF Kuipers, NS Woodling et al. Reversal of Paralysis and Reduced Inflammation from Peripheral Administration of β -Amyloid in TH1 and TH17 Versions of Experimental Autoimmune Encephalomyelitis. Science Translational Medicine 2012; 4: 145ra105-145ra105

Multiple sclerosis (MS), first described in 1868 by Jean-Martin Charcot,[1] is one of the most common cause of neurological disability in young adults. Most patients are diagnosed between the age of 20 and 50. Whereas approximately 2.1 million people are officially living with MS worldwide, this number is obviously underestimated because of the broad spectrum of symptoms and/or there complete absence.[2] MS is described as an autoimmune disorder where auto-reactive immune cells originating from the peripheral circulation home to the CNS, inflicting damage to focal gray and white matter. These resulting demyelinated regions are usually composed of infiltrated lymphocytes and marcrophages believed to cause axonal damage.[3,4] Interestingly, an upregulation of Aβ has been reported in acute and chronic MS lesions, and represents a sensitive immunohistochemical marker of axonal damage.[5,6]

It is well established that extracellular Aβ plaque formation represents the primary histopathological hallmark of Alzheimer disease (AD), and activated microglia,[7] astrogliotic astrocytes,[8] cytokines,[9,10] and some other components of the classical complement pathway[11] are usually found within and around Aβ plaques. Hence, based on the association of Aβ with innate inflammation hallmarks, it was proposed that Aβ might contribute to the destruction of neurons observed in AD. Major efforts are therefore underway to reduce the formation of Aβ plaques (or conversely improve the clearance of Aβ) as a therapeutic strategy.[12-15]

In a recent study published in *Science Translational Medicine*, Grant et al., investigated the implication of Aβ in the pathophysiology of inflammatory demyelinating diseases. Using an animal model of experimental autoimmune encephalomyelitis (EAE), the authors demonstrate against all expectations that peripheral injection of Aβ peptides produces significant protective effect against EAE.[3]

EAE is an animal model most commonly used to study the pathogenesis of autoimmunity, cell trafficking or CNS inflammation and demyelination.[16] EAE is induced either by (1) immunizing animals with myelin-derived proteins or peptides [i.e MOG_{35-55} (myelin oligodendrocyte glycoprotein 35–55) or $PLP_{139-151}$ (proteolipid protein 139–151)] and CFA (Complete Freund's Adjuvant), or by (2) injecting animals with $CD4^+$ T cells specific for myelin-derived peptides ($CD4^+$ T-cell mediated EAE, autoreactive T_H1 or T_H17 cells).[17,18] Interestingly, intraperitoneal (IP) injection (three times per week) of Aβ42 or Aβ40 (i.e., the two main Aβ

species produced upon proteolytic cleavage of the amyloid precursor protein APP by the β-secretase[19]) before the onset of any clinical symptom (i.e., preventive treatment) significantly delayed the occurrence of motor paralysis in $MOG_{35–55}$/CFA injected animals. Reduced severity and incidence of the disease was also observed in Aβ peptides-treated animals. In addition, IP injection of $Aβ_{42}$ or $Aβ_{40}$ peptides after the onset of the symptoms (i.e., curative treatment) significantly extenuated clinical paralysis after 2 to 4 d compare with control saline injected EAE mice, indicating that systemic delivery of Aβ peptides not only prevent the development the of the disease but also reverse EAE symptoms. Furthermore, using an adoptive model of EAE, the authors showed that both Aβ peptides significantly slowdown the progression of EAE symptoms induced by T_H17 and T_H1 cells, indicating that Aβ is able to suppress peripheral T cell-mediated damage against the CNS in vivo.

In most patients, MS appears as a relapsing-remitting disease. Hence, the authors investigated the effect of Aβ in a relapsing-remitting model, inducing EAE with proteolipid protein 139–151 ($PLP_{139–151}$) or adoptive transfer of T_H1-polarized $PLP_{139–151}$ T cells in SJL/J mice. Under these experimental conditions, both Aβ peptides showed a trend for clinical protection in reducing paralysis in mice. Indeed, a significantly reduced CNS inflammation and modulated immunological manifestations of central damage in paralyzed mice was observed in Aβ- vs. vehicle-treated animals. In addition, a decrease in stimulated human and mouse $CD4^+$ T cells proliferation was observed, consistent with in vitro experiments showing that application of $Aβ_{42}$ or $Aβ_{40}$ (50 μg/ml) significantly reduces proliferation of native $CD4^+$ T cells (isolated from buffy coat samples of human donors) by 56% and 43% respectively. Furthermore, a reduced secretion of proinflammatory cytokines IL-2, IFN-β and IL-10 was observed under Aβ treatment. Whereas the cellular mechanism whereby Aβ peptides suppress T lymphocyte function will require further investigation, first results indicate that it might be independent of the T cell activation pathway or cytotoxic effect.

Taken all together, the authors showed that Aβ peptides produce symptomatic beneficial effects in moderating paralysis and reducing brain inflammation in EAE models of MS by suppressing inflammation in lymphoid tissue. Consistent with this observation, EAE induced in APP knockout mice shows a worse clinical manifestation of the disease, possibly due to the absence of Aβ peptides.[3] Interestingly, the two most powerful approved therapeutic drugs against MS [i.e natalizumab (Tysabri®)[20,21] and fingolimod (Gilenya®)[22,23]] are blocking or sequestering lymphocytes outside the CNS, thus preventing their infiltration from the peripheral circulation in the CNS parenchyma,[20,22] suggesting a common cellular mechanism of Aβ and pharmacological agents in reducing MS symptoms. These findings definitively represent important new insights in the physiology and pathophysiology of Aβ in neuronal and inflammatory diseases, and possibly in the development of new therapeutics, despite the fact that some aspects will require further investigation. Indeed, it is well known that due to its hydrophobic properties, $Aβ_{42}$ tends to form fibrils classically found in AD brains.[13] Furthermore, it is believed that mutations that occur near the β-secretase site of APP result in overproduction of Aβ and a shift in $Aβ_{40}/Aβ_{42}$ ratio toward the longer $Aβ_{42}$ peptide, causing early onset AD.[24-27] Although Grant et al. have not found any amyloid deposits in their Aβ-treated animals after three weeks, we cannot exclude that under prolonged treatment period, $Aβ_{42}$ may possibly reach the brain and act as a seed triggering the formation of amyloid plaques. Interestingly, the presence of Aβ specific antibodies have been reported in the serum of AD[28] and MS patients.[29] Although the role of Aβ antibodies remains unknown, they may represent an inbuilt safeguard against amyloid formation. However, patients treated with an active immunization with Aβ vaccine have shown sever signs of meningoencephalitis in phase I clinical trial due to sensitization of Aβ-specific T cells.[30] In the present study, Grand et al. have not found any Aβ-specific T cells in Aβ injected animals, possibly because of the non-formulated Aβ used contrary to the formulated Aβ (AN-1792) use in the clinical trial.[31] Finally, it was recently shown that monomeric Aβ interacts with and modulates NMDA receptor, a process defective in the presence of oligomeric Aβ, causing abnormal calcium influx and possible neuronal damage. Considering the critical importance of calcium signaling in cell physiology, this aspect will required further investigation in the context of Aβ-treated animal.[32]

Overall, the authors have provided precious new insides about the physiological and pathophysiological role of Aβ in MS and AD, bringing a step closer the understanding of what makes Dr. Jekyll to Mr. Hide.

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