Acta Neuropathol (2015) 129:763–766
DOI 10.1007/s00401-015-1416-1

CORRESPONDENCE

Does the difference between PART and Alzheimer's disease lie in the age-related changes in cerebral arteries that trigger the accumulation of Aβ and propagation of tau?

Roy O. Weller[1] · Cheryl A. Hawkes[2] · Roxana O. Carare[1] · John Hardy[3]

Received: 6 February 2015 / Revised: 20 March 2015 / Accepted: 20 March 2015 / Published online: 27 March 2015

Introduction

Primary age-related tauopathy (PART) [7] is characterised by a limited distribution of tau pathology, compared with Alzheimer's disease (AD), and an absence of amyloid-β (Aβ) plaques. Clinically, patients with PART are older and only a minority have profound cognitive impairment. Neurofibrillary tangles (NFTs) containing hyperphosphorylated tau spread in an age-related manner from brainstem to cerebral cortical areas [3] and the presence of Aβ plaques is associated with acceleration in the propagation of NFTs in the pathogenesis of AD [11, 18]. The amyloid cascade [8] appears to drive the hyperphosphorylation and propagation of tau [6, 16] and Aβ oligomers have a toxic effect upon synapses [16].

In the context of PART, we ask the question "Why is there relatively limited spread of NFTs and few if any Aβ plaques in PART compared with AD?" In order to answer these questions, we examine evidence that ageing of cerebral arteries is a trigger for the amyloid cascade and propagation of tau and NFTs. We propose that age-related changes in cerebral arteries impair the perivascular elimination of Aβ and other metabolites from the brain leading to a loss of homoeostasis within the brain, to seeding of plaques of insoluble Aβ and to acceleration of the propagation of tau/NFTs pathology.

✉ Roy O. Weller
row@soton.ac.uk

[1] Neuropathology, Clinical and Experimental Sciences, Faculty of Medicine, Institute for Life Sciences, Southampton University Hospital, University of Southampton, Mail Point 806, Southampton SO16 6YD, UK

[2] Department of Life, Health and Chemical Sciences, Faculty of Science, Open University, Milton Keynes, UK

[3] Reta Lila Research Laboratories and Department of Molecular Neuroscience, UCL Institute of Neurology, London WC1N 3BG, UK

Age-related changes in cerebral arteries, failure of elimination of Aβ and loss of homoeostasis in the brain in Alzheimer's disease

There is an estimated 30 % impairment of clearance of both Aβ42 and Aβ40 from the human brain in sporadic Alzheimer's disease compared to controls but production of Aβ remains the same [12]. Such failure of elimination of Aβ is reflected in the accumulation of soluble and insoluble forms of Aβ in the brain and artery walls with age and AD. Various pathways for the elimination of Aβ have been identified; they include absorption into the blood [26], enzymatic degradation [13], passage into the CSF [19] and lymphatic drainage of Aβ along perivascular pathways in the walls of cerebral capillaries and arteries [5, 9, 17].

Evidence for age-related failure of elimination of Aβ along the walls of blood vessels is derived from experimental studies and observations in human brain tissue. Soluble tracers injected into the brain diffuse through the extracellular spaces and rapidly drain along basement membranes in the walls of cerebral capillaries and arteries to lymph nodes in the neck [4, 23] (Fig. 1a). Aβ produced within the brain parenchyma also drains to cervical lymph nodes [17]. Drainage of solutes, including Aβ, by the perivascular route is impaired with age [9] (Fig. 1b) and by the presence of apolipoprotein E ε4 (APOE4) [10], both of which are major risk factors for sporadic AD. Cerebral amyloid angiopathy (CAA) further impairs perivascular drainage of solutes from the brain [9].

Histological evidence for age-related impairment of perivascular elimination of Aβ from the human brain is

derived from the study of CAA in which Aβ is deposited in the basement membranes in the walls of cerebral capillaries and arteries (Fig. 1c) that form the perivascular lymphatic drainage pathway from the brain [4]. Biochemical studies show a rise in levels of soluble Aβ in the walls of human leptomeningeal arteries between the ages of 20 and 90 years with a sharp rise between 50 and 70 years; thereafter levels decline [22]. As in tracer studies in animals [23], Aβ is not present in the walls of human extracranial internal carotid arteries [22], indicating that Aβ drains to cervical lymph nodes related to the artery at the base of the skull. Biochemical studies also showed a lack of correlation between the presence of histologically or immunocytochemically identified CAA and high levels of soluble Aβ in the walls of arteries [22]. This suggests that it is the age-related changes in artery walls that are important factors in the failure of elimination of Aβ from the brain rather than CAA that tends to appear at a later stage.

The motive force for perivascular drainage of Aβ and other solutes appears to be related to vascular pulsations [1, 21] as revealed by experimental studies showing that reduction of arterial pulsations diminishes perivascular drainage [1]. Furthermore, alterations of vascular tone by denervation result in CAA [2]. As human cerebral arteries age, there is progressive fibrosis and stiffening of the tunica media as reflected in loss of corrugation of the internal elastic lamina [25]. Stiffening of artery walls reduces the amplitude of pulsations in the vessel wall [21] which, together with thickening and biochemical age changes in vascular basement membranes [15], most likely account for age-related failure of perivascular drainage of Aβ and other soluble metabolites from the brain [9].

Although there is direct evidence for age-related impairment of perivascular drainage in mice [9], such data are not available in humans for whom measurements are only available for CSF. In animal studies, 10–15 % of tracer leaks from perivascular drainage pathways into the CSF [23] and this may be the route by which Aβ enters the CSF in humans. Estimates of elimination of Aβ in normal humans suggest that 25 % of Aβ is cleared across the blood–brain barrier and 25 % is cleared through the CSF [19]. It is likely that a high proportion of the remaining 50 % of Aβ is cleared along perivascular pathways but, as yet, no direct data are available.

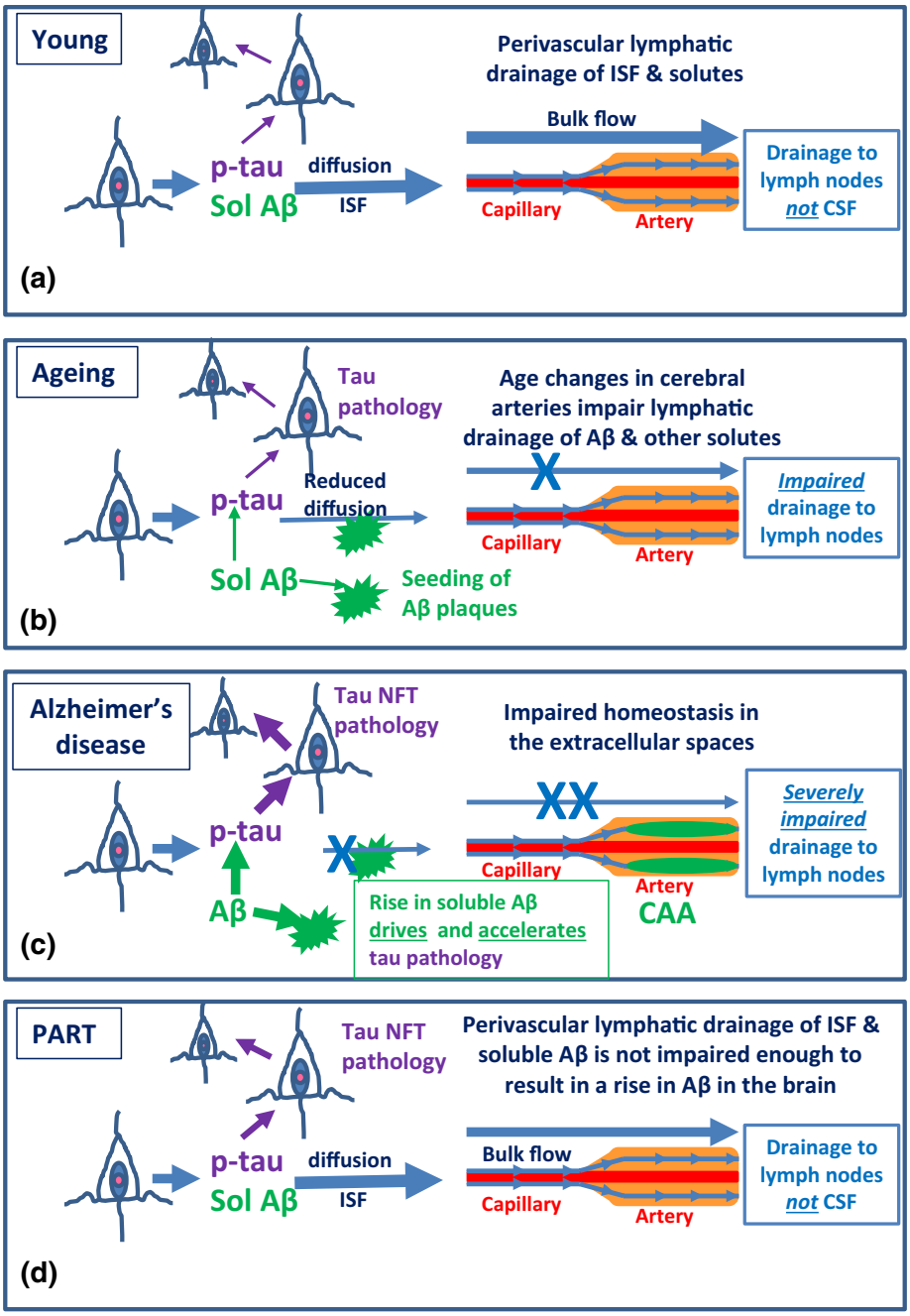
The evidence presented above suggests that one of the primary factors in the failure of elimination of Aβ from the brain is age-related changes in the walls of cerebral arteries due to fibrosis and stiffening of the artery walls and age-related changes in the basement membranes [15, 25]. Deposition of Aβ in the walls of cerebral arteries as CAA appears to be a consequence of age-related impairment of perivascular drainage of Aβ; CAA further impairs perivascular drainage [5, 9].

Fig. 1 Perivascular drainage of Aβ from the brain in the young, with age, in AD and in PART. **a** *Young:* In the brains of normal young individuals, soluble metabolites, such as soluble Aβ, are released into the interstitial fluid (ISF), and diffuse for short distances through the extracellular spaces of the brain parenchyma. Solutes then drain to cervical lymph nodes by bulk flow along basement membranes in the walls of cerebral capillaries and arteries [10] that form the perivascular lymphatic drainage pathways of the brain. Only 10–15 % of ISF draining by the perivascular route leaks into the CSF [23]. The bulk flow pathways are in the basement membranes of cerebral capillaries and arteries (*thin blue arrows*). There is very slow age-related propagation of tau from brainstem to trans-entorhinal regions (*thin purple arrow*). (p-tau: hyperphosphorylated tau). **b** *Ageing:* Changes in basement membranes and fibrosis of artery walls with age and arteriosclerosis result in impairment (X) of perivascular lymphatic drainage of solutes, including soluble Aβ, with impaired homoeostasis in the brain. Impaired drainage results in a rise in the level of soluble Aβ that promotes seeding of insoluble Aβ plaques and starts to drive the hyperphosphorylation and propagation of tau (*thin green arrows*). **c** *Alzheimer's disease:* There is an increasing impairment of diffusion through the extracellular spaces (ECS) due to the presence of Aβ plaques and increasing impairment of perivascular lymphatic drainage resulting from deposition of Aβ in artery walls as cerebral amyloid angiopathy (CAA). As a result, there is further failure of elimination of soluble Aβ leading to an Aβ-driven acceleration of phosphorylation and propagation of tau. Thus tau–NFTs pathology spreads from hippocampus to other areas of the brain in the progression of AD. **d** *PART:* Many unresolved questions remain but it would seem that age-related propagation of NFTs proceeds in PART without Aβ as an accelerating factor. It is probable that any age-related impairment of perivascular drainage of soluble Aβ is insufficient to significantly reduce elimination of Aβ or significantly impair homoeostasis in the brain

Although CAA does not appear to be the primary cause of failure elimination of Aβ but a secondary complication, it acts as a useful marker for failed elimination of Aβ. There is some variation in the severity of CAA between arterial territories. For example, CAA and CAA-related haemorrhages are most common in the occipital and temporal lobes that are supplied by the posterior cerebral artery derived from vertebral and basilar arteries [20]. It appears that different arterial trees show different age-related structural changes with varying effects on the elimination of Aβ and other metabolites.

Loss of homeostasis in the ageing brain and in Alzheimer's disease

The major effect of impaired perivascular drainage is loss of homeostasis. This is reflected in the rise in levels of soluble Aβ and oligomers of Aβ in the brain in AD and the seeding of plaques of insoluble Aβ [18, 24]. However, little is known about the levels of other toxic metabolites in the aged brain that could be harmful to the neuronal environment. Homoeostasis in the brain is maintained by the blood–brain barrier [14] and by the elimination of brain metabolites along a number of pathways including perivascular drainage [4, 23]. There is



evidence for impaired function of the blood–brain barrier in AD [14] and the rise in levels of soluble Aβ is evidence that failure of elimination of soluble metabolites from the ageing brain also contributes to loss of homoeostasis.

It is likely that impaired elimination of Aβ and other metabolites induced by age-related changes in cerebral arteries triggers the rise in soluble Aβ and oligomers that drives the amyloid cascade with seeding of Aβ plaques, hyperphosphorylation of tau and propagation of NFTs.

What might we learn from PART to help understand Alzheimer's disease?

We began with the question "Why is there relatively limited spread of NFTs and few if any Aβ plaques in PART compared with AD?" Answering this question would help us to understand more about AD. It appears from the evidence presented here that age-related changes in cerebral arteries are the trigger for the amyloid cascade, seeding of Aβ plaques and tau propagation. It may be of value, therefore, to compare cases of PART with AD brains to determine (1)

whether there are structural differences in cerebral arteries between PART and AD with less severe age-related changes in PART than in AD and (2) whether levels of soluble Aβ and oligomers in the brains of patients with PART are normal, reflecting normal perivascular elimination of soluble Aβ and maintenance of homeostasis.

The results of further investigations into the role of age changes in cerebral arteries as a trigger for the amyloid cascade could help to direct therapeutic strategies for improving perivascular elimination of Aβ and other metabolites along ageing cerebral arteries in the management of AD.

References

1. Arbel-Ornath M, Hudry E, Eikermann-Haerter K, Hou S, Gregory JL, Zhao L, Betensky RA, Frosch MP, Greenberg SM, Backskai BJ (2013) Interstitial fluid drainage is impaired in ischemic stroke and Alzheimer's disease mouse models. Acta Neuropathol 126:353–364. doi:10.1007/s00401-013-1145-2
2. Beach TG, Potter PE, Kuo YM, Emmerling MR, Durham RA, Webster SD, Walker DG, Sue LI, Scott S, Layne KJ et al (2000) Cholinergic deafferentation of the rabbit cortex: a new animal model of Abeta deposition. Neurosci Lett 283:9–12
3. Braak H, Del Tredici K (2014) Are cases with tau pathology occurring in the absence of Abeta deposits part of the AD-related pathological process? Acta Neuropathol 128:767–772. doi:10.1007/s00401-014-1356-1
4. Carare RO, Bernardes-Silva M, Newman TA, Page AM, Nicoll JAR, Perry VH, Weller RO (2008) Solutes, but not cells, drain from the brain parenchyma along basement membranes of capillaries and arteries. Significance for cerebral amyloid angiopathy and neuroimmunology. Neuropathol Appl Neurobiol 34:131–144
5. Carare RO, Hawkes CA, Jeffrey M, Kalaria RN, Weller RO (2013) Review: cerebral amyloid angiopathy, prion angiopathy, CADASIL and the spectrum of protein elimination failure angiopathies (PEFA) in neurodegenerative disease with a focus on therapy. Neuropathol Appl Neurobiol 39:593–611. doi:10.1111/nan.12042
6. Choi SH, Kim YH, Hebisch M, Sliwinski C, Lee S, D'Avanzo C, Chen H, Hooli B, Asselin C, Muffat J et al (2014) A three-dimensional human neural cell culture model of Alzheimer's disease. Nature 515:274–278. doi:10.1038/nature13800
7. Crary JF, Trojanowski JQ, Schneider JA, Abisambra JF, Abner EL, Alafuzoff I, Arnold SE, Attems J, Beach TG, Bigio EH et al (2014) Primary age-related tauopathy (PART): a common pathology associated with human aging. Acta Neuropathol 128:755–766. doi:10.1007/s00401-014-1349-0
8. Hardy J (2006) Alzheimer's disease: the amyloid cascade hypothesis: an update and reappraisal. J Alz Dis JAD 9:151–153
9. Hawkes CA, Hartig W, Kacza J, Schliebs R, Weller RO, Nicoll JA, Carare RO (2011) Perivascular drainage of solutes is impaired in the ageing mouse brain and in the presence of cerebral amyloid angiopathy. Acta Neuropathol 121:431–443. doi:10.1007/s00401-011-0801-7
10. Hawkes CA, Sullivan PM, Hands S, Weller RO, Nicoll JA, Carare RO (2012) Disruption of arterial perivascular drainage of amyloid-beta from the brains of mice expressing the human APOE epsilon4 allele. PLoS One 7:e41636. doi:10.1371/journal.pone.0041636
11. Lewis J, Dickson DW, Lin WL, Chisholm L, Corral A, Jones G, Yen SH, Sahara N, Skipper L, Yager D et al (2001) Enhanced neurofibrillary degeneration in transgenic mice expressing mutant tau and APP. Science 293:1487–1491. doi:10.1126/science.1058189
12. Mawuenyega KG, Sigurdson W, Ovod V, Munsell L, Kasten T, Morris JC, Yarasheski KE, Bateman RJ (2010) Decreased clearance of CNS beta-amyloid in Alzheimer's disease. Science 330:1774
13. Miners JS, Barua N, Kehoe PG, Gill S, Love S (2011) Abeta-degrading enzymes: potential for treatment of Alzheimer disease. J Neuropath Exp Neurol 70:944–959. doi:10.1097/NEN.0b013e3182345e46
14. Montagne A, Barnes SR, Sweeney MD, Halliday MR, Sagare AP, Zhao Z, Toga AW, Jacobs RE, Liu CY, Amezcua L et al (2015) Blood–brain barrier breakdown in the aging human hippocampus. Neuron 85:296–302. doi:10.1016/j.neuron.2014.12.032
15. Morris AW, Carare RO, Schreiber S, Hawkes CA (2014) The cerebrovascular basement membrane: role in the clearance of beta-amyloid and cerebral amyloid angiopathy. Front Aging Neurosci 6:251. doi:10.3389/fnagi.2014.00251
16. Nisbet RM, Polanco JC, Ittner LM, Gotz J (2015) Tau aggregation and its interplay with amyloid-beta. Acta Neuropathol 129:207–220. doi:10.1007/s00401-014-1371-2
17. Pappolla M, Sambamurti K, Vidal R, Pacheco-Quinto J, Poeggeler B, Matsubara E (2014) Evidence for lymphatic Abeta clearance in Alzheimer's transgenic mice. Neurobiol Dis 71:215–219. doi:10.1016/j.nbd.2014.07.012
18. Price JL, Morris JC (1999) Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. Ann Neurol 45:358–368
19. Roberts KF, Elbert DL, Kasten TP, Patterson BW, Sigurdson WC, Connors RE, Ovod V, Munsell LY, Mawuenyega KG, Miller-Thomas MM et al (2014) Amyloid-beta efflux from the central nervous system into the plasma. Ann Neurol 76:837–844. doi:10.1002/ana.24270
20. Rosand J, Muzikansky A, Kumar A, Wisco JJ, Smith EE, Betensky RA, Greenberg SM (2005) Spatial clustering of hemorrhages in probable cerebral amyloid angiopathy. Ann Neurol 58:459–462
21. Schley D, Carare-Nnadi R, Please CP, Perry VH, Weller RO (2006) Mechanisms to explain the reverse perivascular transport of solutes out of the brain. J Theor Biol 238:962–974. doi:10.1016/j.jtbi.2005.07.005
22. Shinkai Y, Yoshimura M, Ito Y, Odaka A, Suzuki N, Yanagisawa K, Ihara Y (1995) Amyloid beta-proteins 1–40 and 1–42(43) in the soluble fraction of extra- and intracranial blood vessels. Ann Neurol 38:421–428
23. Szentistvanyi I, Patlak CS, Ellis RA, Cserr HF (1984) Drainage of interstitial fluid from different regions of rat brain. Am J Physiol 246:F835–F844
24. Tomic JL, Pensalfini A, Head E, Glabe CG (2009) Soluble fibrillar oligomer levels are elevated in Alzheimer's disease brain and correlate with cognitive dysfunction. Neurobiol Dis 35:352–358
25. Weller RO, Boche D, Nicoll JA (2009) Microvasculature changes and cerebral amyloid angiopathy in Alzheimer's disease and their potential impact on therapy. Acta Neuropathol 118:87–102. doi:10.1007/s00401-009-0498-z
26. Zlokovic BV (2004) Clearing amyloid through the blood–brain barrier. J Neurochem 89:807–811