Pathophysiology of reduced oxygenation of brain tissue in Alzheimer’s disease

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Blood flow and glucose utilisation decline at a very early stage of Alzheimer’s disease (AD), starting in the precuneus and subsequently involving frontal and temporal cortex. We showed previously that the ratio of myelin-associated glycoprotein (MAG, highly susceptible to reduced tissue oxygenation), to proteolipid protein-1 (PLP1, relatively resistant to reduced oxygenation)\(^1\) is significantly reduced in AD frontal cortex, indicating a pathological reduction in perfusion (i.e. reduction exceeding the decline in metabolic demand).\(^2\)

The mechanisms of cortical hypoperfusion in AD are poorly understood. Abnormalities broadly described as ‘cerebrovascular’ are common in AD, over 50% of patients having arteriolarosclerotic small vessel disease (SVD) and over 90% having cerebral amyloid angiopathy (CAA). However, neither of these structural diseases of cerebral blood vessels can account for the distribution and stereotyped progression of pathological hypoperfusion of cerebral cortex in AD.

The accumulation of Aβ in AD is associated with a range of non-structural but nonetheless functionally important changes in the cerebral vasculature. Mechanisms include elevated production of the potent vasoconstrictor endothelin-1 (EDN1),\(^3,5\) upregulation of angiotensin-converting enzyme (which catalyses the production of another vasoconstrictor, angiotensin II),\(^6,7\) inhibition of endothelial nitric oxide synthase activity (reducing endothelial nitric oxide-mediated vasodilatation)\(^8\) and a rise in the production of bradykinin (increasing vascular permeability).\(^9\)

In a previous study, we found the reduction in oxygenation of the frontal cortex in established AD, as indicated by the MAG:PLP1 ratio, to be largely independent of structural vascular disease but associated with elevation in the concentration EDN1.\(^2\)

We have recently analysed precuneus from AD and control brains across the full spectrum of Braak tangle stages and found that MAG:PLP1 was reduced ~50% in early AD (Braak stage III-IV). The reduction showed a weak, although significant, negative correlation with the severity of SVD but a much stronger negative correlation with the concentration of EDN1. EDN1, in turn, correlated highly significantly with both soluble and insoluble Aβ42 (which upregulates neuronal endothelin-converting enzyme-2-mediated production of EDN1)\(^3\) but not with Aβ40. These data suggest that elevated EDN1 production associated with Aβ42-mediated upregulation of endothelin-converting enzyme-2 contributes to pathological cortical hypoperfusion, even in very early AD. More generally, our findings emphasize the importance of not relying solely on morphological methods to elucidate the pathophysiology of ischaemic cerebral abnormalities in dementia.

References