Title. Exploring the pathophysiological role of pericytes in Alzheimer's disease

Theme(s): Neuroscience/Neurology; Medical/Clinical science; Pathology; biochemistry; molecular biology

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Project.

There is a CNS perfusion deficit in Alzheimer's disease (AD). This commences in the precuneus and spreads to other parts of the cerebral cortex. The deficit anticipates the development of dementia, contributes to brain damage, and is caused by both functional and structural abnormalities of the cerebral vasculature. In previous studies we focussed on the role of abnormal arteriolar smooth muscle-mediated vasoconstriction in mediating this hypoperfusion but more recently we have also found evidence of capillary pericytic dysfunction and degeneration, in keeping with the findings of Zlokovic and his colleagues (e.g. Brain Pathol 2014;24:371–86).

Our recent studies indicate that there is a close correlation between the severity of pericyte loss (as evidenced by the decline in platelet-derived growth factor receptor-β level (PDGFR-β)) and the severity of hypoperfusion (assessed biochemically as in our previous studies, by measuring the ratio of myelin-associated glycoprotein to proteolipid protein-1). A reduction in PDGFR-β level was also associated with blood brain barrier (BBB) 'breakdown' (indicated increased fibrinogen level in brain tissue) in AD and was associated with increased Aβ pathology (predicted to be due impaired interstitial drainage). The causes of pericyte degeneration and the mechanisms by which it might contribute to hypoperfusion in AD (if that is the actual direction of causality) are not known.

Aims and Objectives.

The main objectives of this study are (1) to determine the timing of pericyte loss in relation to the onset and regional spread of pathology in AD and (2) to determine the causes of pericyte degeneration in AD.

Methods.

In this PhD the student will perform detailed biochemical assessment of human post-mortem brain tissue (using a range of well-characterised assays) in AD, vascular dementia and age-matched controls to determine the timing, regional distribution and mechanisms of pericyte degeneration in AD. They will also model chronic hypoperfusion and explore the effect of hypoperfusion and Aβ on major trophic signalling pathways in human brain-derived pericyte cultures.

Outcomes.

These studies will provide mechanistic insights into the causes of the pericytic degeneration and the mechanisms by which it might contribute to the pathogenesis of AD.