Progressive endothelial S1PR1 disruption and BBB dysfunction in cerebral microvasculature induced by chronic hypoxic hypoperfusion

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Background: Clinical and neuroimaging studies suggested a fundamental role of BBB leakage in the progressive development of cerebral small vessel disease (SVD) pathology. The capillary barrier and survival are regulated by sphingosine-1-phoshate (S1P) and its receptor isoforms (S1PRs). Disruption of endothelial S1P signalling leads to capillary dysfunction, BBB breakdown, and perivascular inflammation.

Aim: To test the hypothesis that chronic hypoxic hypoperfusion down-regulates capillary endothelial S1P receptor 1 (S1PR1), compromising BBB integrity and leading to neuroinflammation, using a rat model of SVD.

Method: Spontaneously hypertensive stroke-prone rats underwent unilateral carotid artery occlusion (UCAO) followed by a Japanese permissive diet (JPD) for up to 9 weeks. Selective S1PR1 agonist SEW2871 was used to activate S1PR1. MRI, Western blot, and histology were used for measurements.

Results/Conclusions: Significant reduction of endothelial S1PR1 was detected at 4 and 9 weeks following UCAO/JPD onset. The endothelial S1PR1 reduction was also seen in human SVD brains. We also found that significant accumulation of pTau in cortex neurons at 9 weeks, when the rats developed extensive inflammation. The timeline of the accumulation of pTau is consistent with significant reduction of S1PR1 seen at 9 weeks. S1PR1 activation by SEW2781 treatment reduced white matter lesions, preserved cerebral blood flow, and significantly reversed the loss of endothelial tight junction proteins induced by the UCAO/JPD. This protective role of the SEW2871 are associated with changes in PI3K/Akt/Rac signalling pathway. Our data suggest that hypoxic hypoperfusion triggers disruption of S1P-S1PR1 signalling, leading to endothelial injury and BBB dysfunction in SVD.