SNOWBALL

Interplay of amyloid and ischemia and their influence on blood-brain barrier, amyloid transportation systems and neurodegeneration in cerebral amyloid angiopathy (CAA)

Authors: Claudia Borrmann[1], Fabien Gosselet[2], Laurence Tiloy-Fenart[2], Mar Hernandez-Guillamon[3], Anne Mahringer[4], Veronika Chevyreva[1,4], Rick Dickhuizen[5], Maik Derksen[5], Alex Liu[6], Klaus Fassbender[6], Marc Fatar[1]

1 Department of Neurology, University Clinic Mannheim, University of Heidelberg, Germany
2 BBB Laboratory, Faculte des Sciences, Universite D'Artois, Lens, France
3 The Neurovascular Research Laboratory, Vall d'Hebron Research Institute, Barcelona, Spain
4 Institute for Pharmacy and Molecular Biotechnology, Department for Pharmaceutical Technology and Biopharmacy, University of Heidelberg, Germany
5 Biomedical MR Imaging and Spectroscopy Group, Center for Image Sciences, University of Medical Center Utrecht, The Netherlands
6 Department of Neurology, Saarland University, Homburg, Germany

Overview:
Our project elucidate the cross-talk and overlap between amyloid deposition and cerebral ischemia at the blood-brain-barrier (BBB) to understand transporter- and tight-junction-regulation in amyloid pathology. We evaluate endothelial cells, astrocytes, pericytes and microglia and their alterations under ischemic conditions or amyloid stress in-vitro and in animal models of cerebral amyloid angiopathy (CAA). We try to identify targets and mechanism for improving amyloid related human brain diseases.

Methods: We used pericytes and endothelial cells of wildtype mice and cerebral amyloid angiopathy (CAA) mice to study protein expression under ischemic conditions and by adding amyloid protein in-vitro. In animals showing amyloid deposition we analyzed expression of blood-brain-barrier proteins as well as matrix-metalloproteinases (MMP-2 and MMP-9) as well as the role of microglia and alterations of cerebral blood perfusion in older animals. Human brain samples of CAA patients were used to proof experimental findings.

Results: Brain pericytes internalize the amyloid peptides and this internalization is decreased after ischemia stress. This decrease is mediated by a downregulation of receptors interacting with the amyloid peptides such as LRP1.
Ischemia also decreases the expression and activity of amyloid-degrading enzymes such as ECE-1. Ischemia and amyloid stress promote the secretion of inflammatory factors that could alter BBB permeability such as IL1 or I309. Altogether these observations strongly suggest that ischemia decreases amyloid clearance from brain, thus accelerating seniles plaque formation and amyloid neurotoxicity. Lactadherin is accumulated in Aβ-positive vessels in mice and human brains and is abstent in plaques. We have shown an inverse association between serum Lactadherin levels and CSO-EPVS in CAA patients.

Conclusion: Reduced internalization of amyloid by pericytes under ischemic conditions could be one key finding to explain the interplay of ischemia and amyloid pathology. Modulating Lactadherin function is also a potential target for improving therapy of amyloid pathology and especially CAA.