Amyloid Precursor Protein Metabolism at the Blood-Brain Barrier is influenced by Cholesterol and Liver x Receptor Ligands

Cornelia Schweinzer[1], Tatjana Becker[2], Monika Scholler[1], Karoline Etschmaier[1], Michael Holzer[2], Gunther Marsche[2], Ruth Birner Gruenberger[3], Wolfgang Sattler[4], and Ute Panzenboeck[1]

[1]Institute of Pathophysiology and Immunology, [2]Institute of Experimental and Clinical Pharmacology, [3]Core facility for mass spectrometry, [4]Institute of Molecular Biology and Biochemistry, Medical University of Graz, Austria

Several lines of evidence suggest a close relationship between dysregulated lipid metabolism and the development of Alzheimer's disease (AD). Cholesterol and oxysterols, cholesterol-derived ligands of liver X receptors (LXRs), affect processing of amyloid precursor protein (APP) into Aß peptides, which in AD accumulate as amyloid plaques in the brain parenchyma and within cerebral blood vessels. The blood-brain barrier (BBB) may contribute to the etiology of AD via increased import of extracerebral Aß or decreased clearance of cerebral Aß. We aimed at investigating effects of altered cholesterol metabolism on Aß turnover at an *in vitro* model of the BBB. Surprisingly, we found that porcine brain capillary endothelial cells (pBCEC) express and secrete significant amounts of APP. Cholesterol or LXR activation by endogenous (24-hydroxycholesterol, 24-OHChol) or synthetic (TO901317) ligands elevated APP protein expression levels and altered its cellular localization in pBCEC. In parallel 24-OHChol, TO or cholesterol treatment markedly reduced cholesterol biosynthesis from [^{14}C]-acetate and LXR activation enhanced cholesterol esterification in pBCEC. This was accompanied by a down-regulation of HMGCoA reductase, the rate limiting enzyme in cholesterol biosynthesis. A time dependent transport of exogenous, ^{125}I-labeled Aß occurred both from apical to basolateral and vice versa in pBCEC cultured on Transwell filters. We detected albeit low levels of LDL receptor related protein 1 (LRP1) and receptor for advanced glycation end products (RAGE) – predicted transporters for Aß. However, we identified scavenger receptors SREC-1 and SR-AI as other promising candidates which bound fluorescently labeled Aß on transfected BW cells. Altogether our results suggest that APP/Aß production by cerebrovascular endothelial cells might contribute to Aß deposits in AD and can be modified by modulating cellular cholesterol metabolism.