REGULATION OF GENES INVOLVED IN ASTROCYTIC Aβ-UPTAKE AND DEGRADATION BY Aβ ITSELF AND AMYLOID ASSOCIATED PROTEINS

S.D. Mulder1,2, R. Veerhuis1,2,3, M.A. Blankenstein1, H.M. Nielsen4

1Clinical Chemistry and Alzheimer Center, 2Pathology, 3Psychiatry, VU University Medical Center, Amsterdam, The Netherlands, 4Clinical Sciences Malmo, Lund University, Malmo, Sweden

Background: Recently, we found several amyloid associated proteins (AAPs), including a1-antichymotrypsin (ACT), apolipoprotein J (ApoJ), apolipoprotein E (ApoE) and a mixture of serum amyloid P (SAP) and C1q (SAP-C1q) to modify Aβ uptake by astrocytes.

Aim: The aim of this study was to investigate the effect of Aβ and AAPs on the astrocytic expression of genes suggested to be involved in Aβ-uptake and degradation.

Methods: Primary human astrocytes (isolated from control (n=4) and AD (n=4) brain) were exposed to either Aβoligomers or Aβfibrils with or without the above mentioned AAPs. Quantitative gene expression of different Aβ receptors (Scavanger receptor B1 (SCARB1), MARCO and the megalin receptor) and Aβ degrading enzymes (neprilysin, insulin-degrading enzyme (IDE) and metalloproteinase 9 (MMP9) was performed by real time PCR.

Results: Of the analysed genes, only neprilysin, IDE and SCARB1 expression was detectable in the astrocytes. IDE expression was reduced in control astrocytes treated with Aβfibrils together with SAP-C1q (33% reduction, p =0.03)) or ACT (45%, p=0.03). IDE expression was also reduced in AD astrocytes when incubated with Aβfibrils and ApoE (43%, p=0.02). Neprilysin expression increased in control astrocytes upon treatment Aβfibrils with ApoE, and Aβoligomers with ApoE or ApoJ (173%, 337% and 354% increase respectively; p< 0.05). Interestingly, SCARB1 expression was increased in control astrocytes only, when exposed to Aβfibrils with ApoE (70%; p< 0.05) and Aβoligo with SAP-C1q (80%; p< 0.05).

Conclusion: Different forms of Aβ in combination with several AAPs strongly influence the expression of genes involved in Aβ-uptake and breakdown.