INTRACELLULAR APP DOMAIN (AICD) REGULATES SERINE-PALMITOYL-COA TRANSFERASE (SPT) EXPRESSION AND IS AFFECTED IN ALZHEIMER’S DISEASE

S. Grösgen¹, T.L. Rothhaar¹, V.K. Burg¹, B. Hundsdörfer¹, V.J. Haupenthal¹, P. Friess¹, U. Müller², K. Fassbender³, M. Riemenschneider⁴, H.S. Grimm¹, T. Hartmann¹, M.O.W. Grimm¹

¹Neurobiology, Saarland University, Homburg, ²Institute for Pharmacy and Molecular Biotechnology (IPMB), University of Heidelberg, Heidelberg, ³Neurology, ⁴Psychiatry, Saarland University, Homburg, Germany

Introduction: Lipids are crucially involved in the progression of Alzheimer’s disease (AD) as risk or protective factors. Recently, changes in sphingolipid metabolism have been linked to AD. The key enzyme in sphingolipid metabolism is serine-palmitoyl-CoA transferase (SPT) which catalyses the de novo synthesis of ceramide.

Aims: In this study we investigated a potential physiological function of the amyloid precursor protein (APP) and its intracellular domain (AICD) in sphingolipid homeostasis.

Methods: To elucidate the effect of APP and AICD on SPT activity and gene expression we analysed APP deficient mouse embryonic fibroblasts (MEF) and APP knock-in MEF cells expressing an APP construct, that lacks the last 15 amino acids from the C-terminus (MEF APPΔCT15) and the according mice model by real time PCR (RT-PCR) analysis and a specific enzymatic assay to determine SPT activity. AD relevance of SPT gene expression was confirmed using human post mortem brains and corresponding controls.

Results: APP intracellular domain (AICD) was found to decrease gene expression of SPT subunit 2, which represents the catalytic subunit of the SPT heterodimer. Further, AICD induced gene expression was linked to the presence of the adaptor protein Fe65.

Conclusions: Altered SPT levels in AD post mortem brains suggest a possible role for SPT in AD pathology. In conclusion, we demonstrate that AICD is capable to decrease SPT expression, the rate limiting enzyme in sphingolipid metabolism, which is affected in AD pathology.

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