PLASMALOGEN SYNTHESIS IS REGULATED VIA ALKYL-DIHYDROXYACETONEPHOSPHATE-SYNTHASE (AGPS) BY AMYLOID PRECURSOR PROTEIN (APP) PROCESSING AND IS AFFECTED IN ALZHEIMER'S DISEASE

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Introduction: Lipids play an important role as risk or protective factors in Alzheimer's disease, which is characterized by amyloid plaques composed of aggregated amyloid-beta (Aβ). Plasmalogens are major brain lipids and controversially discussed to be altered in Alzheimer's disease (AD).

Aims: Here we investigate a new physiological function of the amyloid precursor protein (APP) in plasmalogen metabolism.

Methods: To quantify the effect of the APP intracellular domain (AICD) in vivo and in vitro on the expression of the alkyl-dihydroxyacetonephosphate-synthase (AGPS), a rate limiting enzyme in plasmalogen synthesis, we performed Real-time PCR experiments. Additionally protein levels of the AGPS and ROS level were analyzed. Plasmalogens were detected by mass spectrometry. To elucidate these questions Presenilin and APP deficient cells, cells expressing APP, which lacks the AICD domain, and the according mice models were analyzed. AD relevance was confirmed in human post mortem and control brains.

Results: APP intracellular domain (AICD) was found to increase the expression of the AGPS. Alterations in APP dependent changes of AGPS expression result in reduced protein and plasmalogen levels. Under the pathological situation of AD, increased Aβ level lead to increased reactive oxidative species (ROS) production, reduced AGPS protein and plasmalogen levels. Accordingly, phosphatidylethanol plasmalogen (PE-PL) was decreased in the frontal cortex of AD compared to age matched controls.

Conclusion: Our findings elucidate that plasmalogens are decreased as a consequence of AD and regulated by APP processing under physiological conditions.

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