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Identification of new modulators of APP processing and Amyloid beta peptide production in the context of Alzheimer's disease

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The earliest pathological change in Alzheimer's disease (AD) is the deposition of amyloid-beta peptides (Aβ) of 38-43 residues length into senile plaques in the brain, which initiates a pathological cascade that leads to impaired cognitive function and dementia. While Aβ1-40 is the primarily produced peptide, the senile plaques consist mainly of the particularly aggregation-prone Aβ1-42, Aβ1-43 and the N-terminally truncated Aβ4-42 peptides. The inhibition of the γ-secretase protease that is responsible for Aβ production has been among the most pursued therapeutic strategies in AD. However, γ-secretase has many other substrates than APP and clinical studies with γ-secretase inhibitors (GSIs) have revealed severe side effects. The here presented work has set the focus on the identification of endogenous γ-secretase modulators, which specifically modulate the processing of APP and Aβ production, without interfering with the processing of other γ-secretase substrates. First, we found that the lipid composition surrounding the γ-secretase complex plays an important role for the stability and activity of the intramembrane cleaving protease, which offers the possibility of modulating Aβ production via the composition of nutritional lipids. We then show that the endogenous biometals zinc and copper differentially modulate Aβ production by hitherto unknown mechanisms. Copper directly targets the protease γ-secretase, while zinc is inducing dimerization of the γ-secretase substrate APP-C99, thus precluding the release of Aβ peptides from APP-C99. Apart from inhibition of total Aβ production, we found that at lower zinc concentrations the processing of APP-C99 is only partially inhibited and the processing shifts towards an increased production of the toxic peptide Aβ1-43. The effects of zinc on Aβ metabolism and catabolism are manifold and we found that APP cleavage of the secreted, zinc-dependent ADAMTS4 protease, generates the N-terminally truncated peptide Aβ4-42, that is highly abundant in senile plaques and whose origin was previously unknown. The differential processing of APP outside of the pro-amyloidogenic pathway presents a promising strategy to inhibit Aβ production and our lab has previously discovered that the adipocyte plasma membrane associated protein (APMAP) associates with the γ-secretase complex and modulates APP trafficking and Aβ production trough the autophagy-lysosomal system. Intriguingly, while APMAP is widely expressed in the brain, the biological function of APMAP in the brain has been totally unexplored so far. We have generated the first full APMAP-KO mouse line and found impaired spatial memory phenotypes in those mice. Importantly, in an AD mouse model, APMAP-KO worsened cognition and increased the deposition of senile plaques in the hippocampus. To better understand the mechanism behind this observation, we next purified APMAP protein-complexes under native conditions and characterized the APMAP interacting proteins (AIPs) by mass spectrometric analysis. Interestingly, several of the identified AIPs have important roles in the autophagy-lysosomal system and we found in cell-based assays that several AIPs also modulate APP processing and Aβ production, suggesting that this alternative pathway of APP processing could potentially be targeted for a therapeutic intervention in AD. Importantly, we also found reduced expression of two AIPs and a drastic increase of a previously uncharacterized APMAP splicing variant (APMAP2) in the cortical lysates of humans with advanced-stage AD. The development of sporadic AD is multifactorial and little is known about environmental risk factors. In light of this, we found that the pesticide fipronil and its metabolites are shifting Aβ production towards the amyloidogenic Aβ42 and Aβ43 peptides, suggesting that those pesticides could be environmental risk factors that contribute to the increasing global burden of AD.

Jury: Dr. Patrick C. Fraering (thesis supervisor), Prof. Dr. Urs E. Albrecht (thesis co-supervisor), Prof. Dr. Nicolas Toni (external co-examiner), Prof. Dr. Beat Schwaller (internal co-examiner), Prof. Dr. Louis-Félix Bersier (president of the jury).