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Studies on Pyroglutamate-Modified Abeta and Glutaminyl Cyclase in Mouse Models of Alzheimer's Disease

In the present work, two novel antibodies that were generated at the laboratory of Prof. Bayer against AβN3pE peptides were tested and proven in terms of their specificity and sensitivity. Afterwards, one of these antibodies was used to evaluate plaque load of AβN3pE versus generic Aβ plaque load in two mouse models of AD. The area of AβN3pE plaques demonstrated 23.3% and 17.2% of the generic Aβ plaques area in the frontal cortex of the APP/PS1KI and the 5xFAD mouse models respectively by 6 months of age. In addition to the high AβN3pE plaque burden, 5xFAD female mice showed spatial working memory impairment and reduced anxiety at 6 months of age. These observations point out that the 5xFAD mouse model represents a potential model to study the role of AβN3pE in the pathology of AD.

In order to study the effect of QC on AD pathology, the 5xFAD/hQC mouse model was generated. In addition to QC overexpression, the 5xFAD/hQC model presented generic Aβ plaques and AβN3pE plaque deposition in many brain regions. QC and APP stainings were found to be localized in the same intracellular compartments within neuritic plaques which might enable QC role in modifying the Aβ peptides to generate AβN3pE. However, in order to assess the effect of QC on plaque pathology, a statistically valid comparison between the 5xFAD and 5xFAD/hQC plaque load I required. To do this, testing statistically sufficient animal numbers should be performed in the future.

The preliminary experiments showed that 5xFAD/hQC mice developed spatial working memory and motor coordination impairments by 6 months of age, however at this age there was no difference to hQC mice alone. As a future outlook, increasing the size of the experimental groups is required to assess a potential QC effect on AD pathology. Moreover, adding the behavioral tests at later time points such as 9 months of age can further support the findings at 6 months and shed the light on other age-dependent behavioral impairments which might require more time to appear. Besides, including other tests such as the open-field maze and the rotarod task might reveal the reasons behind decreased arm entries and declined motor coordination in these mouse models. Taken together, behavioral and histological observations indicate the possibility of using the 5xFAD/hQC to study the effect of QC and AD pathology which is still not clear at the moment and needs to be studied in more detail.