INCREASED HIPPOCAMPAL SENSITIVITY TO EPILEPTIFORM ACTIVITY IN ONE MONTH OLD TgCRND8 MICE: CORRELATION WITH THE LEVEL OF βCTF EXPRESSION

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Introduction: Increased sensitivity to seizures in transgenic mouse models of Alzheimer's disease (AD) occurs before amyloid-β (Aβ) plaque formation and has been related to altered excitability of hippocampal neuronal networks. However, the underlying mechanisms and the precise Aβ-related molecular species involved remain unknown.

Aim: To investigate if the susceptibility to epileptiform activity is correlated with the level of Aβ-precursor protein (APP) maturation products in the hippocampus of 1-month-old TgCRND8 mice, a model of AD.

Methods: Whole hippocampal preparations from 1-month-old TgCRND8 mice were used for the field potential recordings in the CA1-subiculum area. The susceptibility to epileptic activity was tested by bath application of 20µM bicuculline over 15 min. APP, βCTF, Aβ and its oligomerization products were quantified by western blot with 6E10 and CT-20 antibodies.

Results: Bicuculline triggered a 2.5 fold increase in the number of epileptic bursts in TgCRND8 compared to wild-type mice (141+/−10 versus 33+/−4 bursts over the 15 min application, respectively; n=3 per genotype). βCTF was the main APP cleavage product found in 1-month-old TgCRND8 mice. By contrast, Aβ monomers and likely trimers were not detectable before plaque expression, which occurs at 4 months of age in TgCRND8 mice.

Conclusion: Increased hippocampal susceptibility to epileptiform activity in pre-plaque TgCRND8 mice might be related to βCTF rather than to soluble Aβ. Since some pre-inflammatory alterations occur in young TgCRND8 mice, we now aim to determine if these changes are related to increased βCTF expression and hippocampal excitability.