Impairment of spatial and associative learning in APP transgenic mice

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Deposition of -amyloid (A) peptide in the brain is a major pathological feature of Alzheimer's Disease (AD). Transgenic mice (TgCRND8) encoding a double mutated allele of human APP genes (Swedish; KM670/671NL+Indiana; V717F) show increased levels of A and develop extracellular amyloid deposits (plaques) in the brain from 3 months of age onwards. We tested F1 B6/129.TgCRND8 cohorts of TgCRND8 mice at ages of 2 months (pre-plaque stage); 3 months (plaque formation); and 5 months (potent deposition of plaques) in reference memory water maze (WM) and conditioned taste aversion (CTA; i.e. learning the association between novel taste and induced nausea) tests to (1) demonstrate the profile of the onset of cognitive impairment in TgCRND8 mice, and to (2) appraise behavioral markers associated with A accumulation and plaque deposition. The results demonstrated that the onset of progressive changes in cognitive function in TgCRND8 mice parallel those seen in AD. Both 2 month-old Tg and non-Tg mice showed comparable reference memory. Spatial reference memory loss associated with hippocampal damage occurred at 3 months of age, and progressed further at 5 months. This cognitive impairment was associated with increased levels of detergent soluble A, while the insoluble (formic acid extracted) A levels showed only weak association. Analysis of search strategies in WM revealed that impaired Tg mice searched for the platform primarily using a non-spatial, chaining strategy. Implicit memory under cortical control tends to be affected later in humans, and correspondingly the impairment in association of taste aversion was seen only in 5 month-old Tg mice. Whether deficits in these cognitive systems are correlated with amyloid plaque burden remains to be determined.