CHOLINERGIC HYPOFUNCTION THREATENS APP PROCESSING AND HIPPOCAMPAL INTEGRITY
OF TG2576 MICE

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Introduction: Early Alzheimer’s disease (AD) is characterized by loss of basal forebrain cholinergic neurons (BFCN), marked hippocampal atrophy as well as amyloid plaques and neurofibrillary tangles in cortical and limbic areas. Cholinergic hypofunction has been long assumed to contribute to cognitive decline. Recently, experimental data from genetically deletion of different types of cholinergic receptors have demonstrated its involvement in amyloidogenic APP processing.

Aims: We used the cholinergic immunotoxin mu p-75 saporin on Tg2576 mice to closely emulate the loss of BFCN observed in AD and, therefore, study the interactions between cognition, cholinergic hypofunction, APP processing and hippocampal integrity.

Methods: Lesioning was carried out by stereotaxic i.c.v. microinjection of the toxin. Two weeks following lesion, mice were subjected to behavioural tests, and subsequently brains were examined for biochemical analysis.

Results: Cholinergic hypofunction induced significant memory deficits in the Morris water maze and novel object recognition test accompanied by a significant 14-fold increase in levels of soluble Aβ1-42. This increase did not unleash increased amyloid plaque load but intracellular deposition. Cholinergic hypofunction decreased expression of the a-secretase ADAM17, which might explain the switch towards amyloidogenic processing of APP. Tg2576 mice with cholinergic loss showed reduction in hippocampal volume that was accompanied by dying neurons, as well as by increased reactive astroglialosis, even 1 month after immunolesion.

Conclusions: Together these data demonstrate that BFCN provides control over APP processing and neurotrophic input into hippocampus. Thus, drugs aimed at favouring cholinergic transmission should be still consider as a valuable treatment for AD.