CHF5074 restores visual memory ability and rescue synaptic dysfunction in pre-plaque Tg2576 mice

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Synaptic dysfunction is an early event in Alzheimer's disease (AD) and occurs before the formation of amyloid plaques and neurofibrillar tangles (Schliebs and Arendt, 2011). In particular, the appearance of cholinergic neuritic dystrophy, i.e. aberrant fibers and fiber swelling are widely common in AD (Schliebs and Arendt, 2011). It has been recently suggested that memory impairment in plaque-free Tg2576 mice may be due to cholinergic synapse dysfunction rather than amyloid plaque deposition (Watanabe et al., 2009). Thus, we used Tg2576 mice to compare the effects of CHF5074, a drug which attenuates memory deficit in AD transgenic mice (Imbimbo et al., 2010), and LY450139 (semagacestat) on in vivo novel object recognition test, on in vitro [³H]acetylcholine and GABA release mice and on in vivo dialysate glutamate levels in pre-plaque (7 month-old) Tg2576.

Vehicle-treated Tg2576 mice displayed an impairment of recognition memory compared to wild-type animals. This impairment was recovered in transgenic animals acutely treated with CHF5074 (30 mg/kg), while LY450139 (1-10 mg/kg) was ineffective. In frontal cortex synaptosomes from vehicle-treated Tg2576 mice, K⁺-evoked [³H]acetylcholine release was lower than that measured in wild-type mice. This reduction was absent in transgenic animals sub-acutely treated with CHF5074 (30 mg/kg daily; 8 days), while it was slightly, not significantly, amplified by LY450139 (3 mg/kg daily; 8 days). There were no differences between the groups on spontaneous [³H]acetylcholine release as well as on spontaneous and K⁺-evoked GABA release. Microdialysis experiments indicated that the sub-acute treatment with CHF5074 (30 mg/kg/day; 8 days) or LY450139 (3 mg/kg/day; 8 days) did not affect basal glutamate levels in wild-type or Tg2576 mouse prefrontal cortex. However, CHF5074 reduced while LY450139 increased dialysate glutamate levels in Tg2576 mice.

These results suggest that the positive effect of CHF5074 on learning and memory in pre-plaque Tg2576 mice is associated with the restore of K⁺-evoked acetylcholine release from cortical nerve terminals, which is decreased in vehicle-treated Tg2576 compared to wild-type animals. In addition, the administration of CHF5074 and LY450139 induces opposite effects on prefrontal cortex extracellular glutamate levels in Tg2576 mice, thus confirming the different neurochemical profile of action of the two compounds in 7 months old Tg2576 mice (Giuliani et al. 2013). Taken together, these findings suggest CHF5074 as a possible candidate for early AD therapeutic regimens.

Watanabe et al. (2009). Brain Res. 1249, 222-228.
Imbimbo et al. (2010), J. Alzheimers Dis. 20, 159-73.