CHF5074 (CSP-1103) induces microglia alternative activation in plaque-free tg2576 mice and primary glial cultures exposed to beta-amyloid

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Activation of microglia associated with neuroinflammation and loss of phagocytic activity is considered to play a prominent role in the pathogenesis of Alzheimer's disease (AD). CHF5074 (CSP-1103) has been shown to reduce brain inflammation in patients with mild cognitive impairment. CHF5074 was also found to improve recognition memory and hippocampal LTP when administered to plaque-free Tg2576 mice (5-month-old) for 4 weeks. We studied the effect of CHF5074 on the expression profile of proinflammatory (M1) and anti-inflammatory/phagocytic (M2) microglia in astrocyte-microglia cultures exposed to beta-amyloid 1-42 (Aβ) and in brain of 5-month-old Tg2576 mice treated with CHF5074 (375 ppm) for 4 weeks.

In astrocyte-microglia cultures exposed to 10μM Aβ, CHF5074 totally suppressed the Aβ -induced the pro-inflammatory expression of IL-1β, TNFα and iNOS mRNAs. Furthermore, CHF5074 significantly increased mRNA levels of the M2 anti-inflammatory Mannose Receptor type C 1 (MRC1/CD206) and Triggering Receptor Expressed on Myeloid cells 2 (TREM2). The effect of CHF5074 was not reproduced by ibuprofen or R-flurbiprofen, as both compounds did not modify the anti-inflammatory/phagocytic transcription.

In the hippocampus of 5-month-old Tg2576 mice we detected no increase of pro-inflammatory gene transcription, when compared to wild-type littermate, but a significant reduction of M2-related genes MRC1/CD206, TREM2 and the chitinase-3 like 3 (Ym1) expression. CHF5074 treatment did not modify M1 transcription but significantly increased expression of MRC1 and Ym1. CHF5074 effects appeared to be hippocampus-specific, as the M2 transcripts were only slightly modified in the cerebral cortex.

CHF5074 specifically drives the expression of microglia M2 markers either in young Tg2576 hippocampus or in primary astrocyte-microglia cultures, suggesting its potential therapeutic efficacy as microglial modulator in the early phase of AD.