A flavonoid gamma-secretase modulator (GSM) reduces beta-amyloid and tau pathologies in the AD mice

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A flavonoid gamma-secretase modulator (GSM) reduces beta-amyloid and tau pathologies in the AD mice

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Research Abstract

? DESCRIPTION (provided by applicant): There may be a dual role of ?-secretase in AD. The

cleavage of APP by ?-secretase is key in the pathogenesis of AD and amyloid accumulation in the brain. As such, ?-secretase has been targeted for years for development of AD therapies and ?-secretase inhibitors (GSIs). Most recently it was shown that a mutation in presenilin affecting ?-secretase activity may impair microglial phagocytosis of Aß and promote amyloid accumulation. Because GSIs may impair salutary microglia activity via inhibition of Notch signaling pathway, we seek to develop a new class of flavonoids GSIs that can reduce ?-APP cleavage yet minimize their potential negative effect on microglia phagocytosis activity. Optimally we would seek to do the former while promoting the latter. Turning to diosmin's efficacy as promoting both anti-amyloidogenic APP processing and microglial phagocytosis of Aß, we have recently shown that the treatment of Tg2576 mice with diosmin markedly reduces cerebral Aß40,42 species and consequently lowers Aß deposits. Based on this finding, its diosmetin metabolite becaome our focus on preliminary studies. These results indicate that diosmin/diosmetin not only reduces Aß by inhibiting ?-APP cleavage and decreases hyperphosphorylated tau by modulating GSK3ß activation, but also enhances microglial phagocytotic phenotype switching. In this proposal, flavonoid-diosmin will be orally administered to 3XTg-AD mice before (prophylactic treatment group) or after (therapeutic treatment group) development of AD-like pathology. Groups of untreated non-transgenic littermates will be compared to the transgenic treatment groups. Oral administration of diosmin to 3XTg-AD mice at 4 and 6 months of age will be performed for 6 months. Aim 1, we will sacrifice these mice at several ages to examine histological and biochemical endpoints and correlate pathological changes with improvement of cognitive impairment (funded by NCAAM). In this study, we plan to evaluate two time points comparing diosmin to control. Groups will be compared by their effects on opposing cognitive impairment and reducing AD-like pathology, including cerebral ß-amyloid deposits and tau hyperphosphorylation/NFT. AD is known to be accompanied by up-regulation of pro-inflammatory microglial responses manifested as the increased chemokine production by microglia. In addition, our preliminary data show that diosmin's metabolite, diosmetin induces anti-inflammatory phenotype through down-regulation of microglial CD40 signaling and resultant promotion of microglial phagocytosis of the aged Aß peptide. Thus in Aim 2, we will test the hypothesis that diosmin treatment preserves the pro-inflammatory phenotype in primary microglia isolated from young and aged 3XTg-AD mice. These studies could lay the foundation for AD clinical trials with diosmin diet supplementation in the near future.

Further information available at:

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