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Long-term Centella asiatica treatment improves cognition, increases synaptic and antioxidant markers and reduces plaque burden in β-amyloid overexpressing mice

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Keywords

beta-amyloid, NRF2, antioxidant, synaptic plasticity

Abstract

Objectives

We have previously reported that short-term treatment with the water extract of Centella asiatica (CAW) activates the endogenous antioxidant response pathway and ameliorates cognitive deficits without altering plaque burden in mouse models of β-amyloid (Aβ). Here we investigate whether prolonged CAW exposure in 5xFAD mice has similar effects on cognitive function and Aβ pathology, in addition to markers of antioxidant response and synaptic plasticity. We also used primary neurons isolated from 5xFAD mice to explore how the antioxidant response pathway contributes to these effects.

Methods

4-month-old male and female 5xFAD mice and wild-type (WT) littermates were treated with CAW (2g/L) in their drinking water for three months prior to one month of behavioral tests of learning, memory and executive function after which mice were sacrificed and expression of antioxidant and synaptic genes was assessed and Aβ plaque burden was quantified. Additionally, markers of synaptic plasticity and oxidative stress were evaluated in primary neurons treated with CAW and the NRF2 inhibitor ML385.

Results

Long-term treatment with CAW improved cognitive performance in 5xFAD animals. CAW also increased synaptic and antioxidant gene expression and reduced Aβ plaque burden. Interestingly, while this decrease in pathology was evident in the cortex of both male and female mice, only female animals also showed a reduction in plaque burden in the hippocampus. Additionally, CAW induced expression of NRF2-reduced oxidative

stress in primary neurons from 5xFAD animals and enhanced synaptic plasticity, but this effect was abrogated when cells were co-treated with CAW and ML385.

Conclusion

These data indicate that long-term CAW treatment in 5xFAD mice can attenuate cognitive impairment, increase antioxidant and synaptic gene expression, and alter Aβ plaque burden. This combined with the in vitro data suggest that the activation of the antioxidant transcription factor NRF2 may play an important role in these effects.