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CD74 inhibitor DRhQ improves cognition and mitochondrial function and reduces neuroinflammation in 5xFAD mouse model of Aβ accumulation

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Abstract

Background

Neuroinflammation and mitochondrial dysfunction are early events in Alzheimer's disease (AD) and contribute to neurodegeneration and cognitive impairment. The CD74-MIF (macrophage migration inhibitory factor) axis is a mediator of the neuroinflammatory response. DRhQ competitively inhibits MIF-CD74 binding and elicits beneficial effects in other neurodegenerative disease models. Here we evaluate its effects in β-amyloid (Aβ) overexpressing mice.

Methods

5xFAD mice and their wild type littermates were treated with DRhQ (100 µg) or vehicle for 4 weeks. In the fourth week, mice underwent cognitive testing and Aβ pathology, microglial activation, mitochondrial function and expression of mitochondrial and inflammatory markers was analyzed.

Results

DRhQ improved recognition memory, reduced Aβ plaque burden and microglial activation and attenuated mitochondrial dysfunction in the brains of female 5xFAD mice. Similar, but non-significant, effects were observed in male 5xFAD mice treated

with DRhQ. No differences in the cortical expression of mitochondrial or inflammatory genes were seen with DRhQ treatment.

Conclusions

These data suggest that DRhQ is beneficial in female 5xFAD mice. Future studies are needed to elucidate the reason for this possible sex-dependent response as well as to optimize the dose, and timing of DRhQ treatment and gain a better understanding of its mechanism of action.