GM6 attenuates activated cofilin and β-arrestin2 impact on pathological tau and decreasing tau aggregates in Alzheimer's disease (AD) and frontotemporal lobar degeneration (FTLD)

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Introduction

Alzheimer's disease (AD) and frontotemporal lobar degeneration (FTLD) are major causes of dementia in the elderly. Recent studies have implicated both activated-cofilin and b-arrestin2 in the pathogenesis of AD and FTLD. The deposition of amyloid β (Aβ) peptide into amyloid fibrils and hyperphosphorylated tau into neurofibrillary tangles (NFTs) are key processes in the pathogenesis of the diseases. Recent studies have shown that activated cofilin and β-arrestin2 are increased in the brains of patients with AD and FTLD, associating them in the disease process. In addition, studies have shown that reduction in cofilin and β-arrestin2 in vitro and in vivo reduces the impact on AD and FTLD. GM6 is a derivative of motoneuronotrophic factor (MNTF) which functions as a regulator of key biomarkers, acts upon multiple extracellular receptors to modulate a series of signaling pathways. GM6 has been tested in various clinical trials and shown to be safe with favorable shifts in blood biomarkers of Ab, tau, TDP-43, and SOD1 as well as positive signals of clinical outcomes.

Objectives

Our studies have focused on the role of GM6 in the mitigation of AD pathogenesis. APP/PS-1 and tau transgenic mice were treated with GM6 daily for up to 3 months and examined for changes in Aβ peptide levels, plaques, inflammation, and tau (p-tau), as well as behavioral changes associated with disease progression. We also determined the impact of GM6 on cofilin (Cof) and β-arrestin2 (Arr) levels by Western blots in the brain of APP and tau mice.

Methods

Both APP/PS-1 and hTau transgenic mice were aged 6-8 months and then treated with the various doses of GM6 (1 – 5 mg/kg or vehicle daily for 3 months. At the end of the treatment, the mice were tested behaviorally and euthanized. The brains were taken (1/2 fixed, ½ frozen) and processed for immunohistochemistry or western blot analysis. Tissues were used for westerns for cofilin and β-arrestin2, as well as Aβ, p-tau, inflammatory markers, etc.

Results

Our results show that when APP transgenic mice were treated with GM6 at the beginning of plaque formation, Aβ peptide levels were diminished, plaque load attenuated, and inflammation was reduced. In the tau mice, when GM6 was treated at the beginning of p-tau formation, tau levels were reduced, p-tau was lessened, and inflammation was moderated. In both transgenic mice, behavioral changes were attenuated in the GM6 treated mice. In addition, in both the APP and tau mice, cofilin and β-arrestin2 levels decreased by ~80% in the brains, and amyloid plaques decreased by 60%, and p-tau was reduced by 70%. In both the APP and h-tau mice, inflammation cytokines TNF-α, IL-1β, IL-6 and TGF-β were significantly reduced (~80-90%). The data suggest that GM6 has a significant impact on AD and tauopathies partly by mediating changes in cofilin and b-arrestin2.

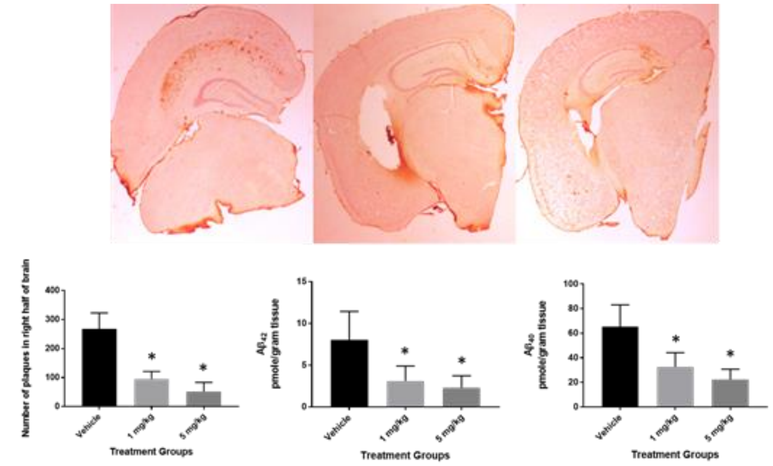

Figure 1. APP/PS-1 tg mice treated with GM6. Mice were treated with GM6 at the indicated doses and examined for Aβ peptides and plaques. N=10, *p<0.0001.

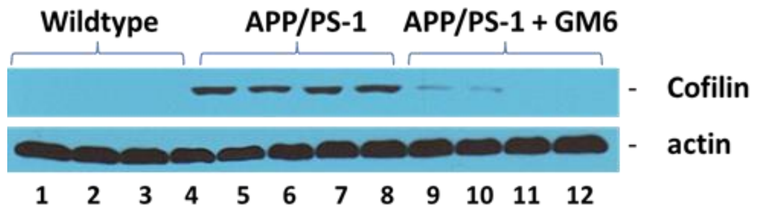

Figure 2. APP/PS-1 tg mice treated with GM6. Mice were treated with GM6 at the indicated doses and examined for Cofilin levels in the brain. N=10, *p<0.0001.

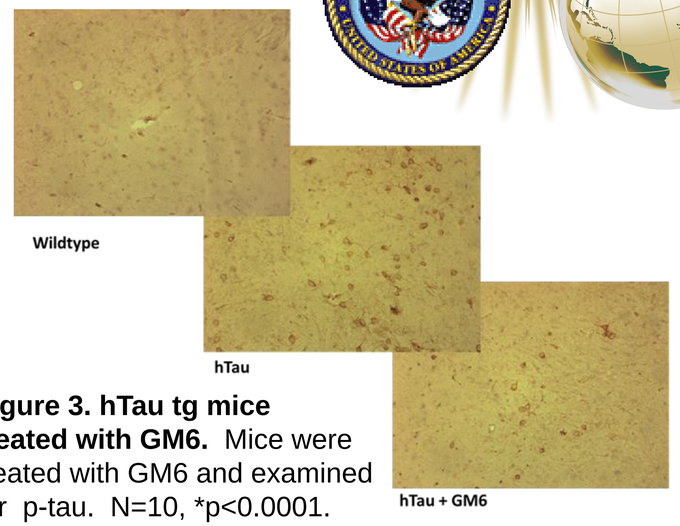

Figure 3. hTau tg mice treated with GM6. Mice were treated with GM6 and examined for p-tau. N=10, *p<0.0001.

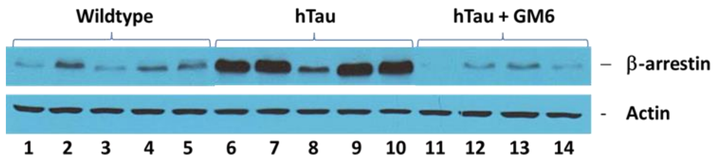

Figure 4. hTau tg mice treated with GM6. Mice were treated with GM6 and examined for β-arrestin2 levels in the brain. N=10, *p<0.0001.

Discussion

In conclusion, these findings suggest that GM6 may be a feasible approach to attenuate AD and FTLD pathology as a combination therapy by concurrently reducing inflammation, activated cofilin, β-arrestin2, Aβ and hyperphosphorylated tau.

Implications

The proposed studies determined the role of GM6 in the control of cofilin and β-arrestin in the brain in Ad and tauopathies. In addition, these studies may provide a better understanding as to the implications in other neurodegenerative disorders.

References

Yu J, Zhu H, Taheri S, Mondy W, Kirstein C, Swindell WR, Ko D, Kindy MS. GM6 attenuates Alzheimer's disease pathology in APP mice. Molecular Neurobiology. 2019;56:6386-6396.