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GM6 attenuates inflammation in Alzheimer's disease pathology via modulation of fibrinogen by reducing Aβ and tau

Mark S. Kindy, Ph.D., FAHA
Professor, Department of Pharmaceutical Sciences
Senior Research Career Scientist, Haley VAMC

GENERVON

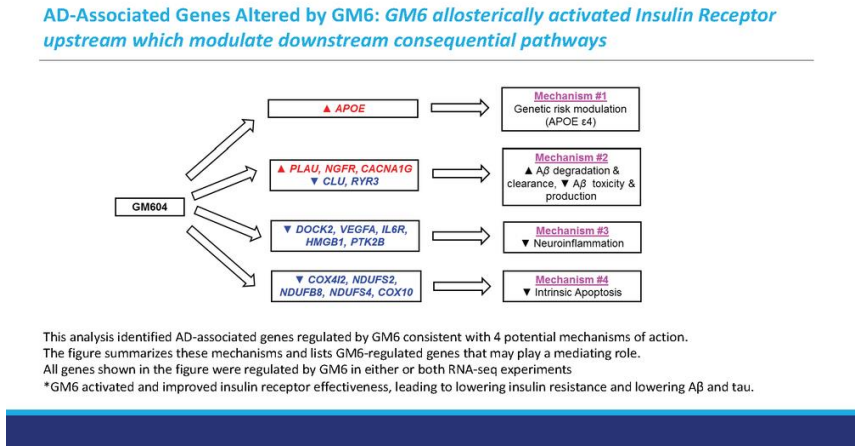
Motoneuronotrophic Factor (MNTF)

Alzheimer's disease/GM6

Alzheimer's disease (AD) results in the deposition of amyloid β (Aβ) peptide into amyloid fibrils and tau into neurofibrillary tangles. Fibrinogen has been shown pleiotropic roles in the activation of CNS inflammation.

GM6 is a derivative of motoneuronotrophic factor (MNTF) which functions as a regulator of key biomarkers. GM6 is neither an antibody nor a single-target agonist or antagonist. GM6 has been shown to be safe and tolerable in four clinical trials. The Phase 2A ALS clinical trial showed favorable shifts in blood biomarkers of tau, TDP-43, and SOD1, as well as positive signals of clinical outcomes.

GM6 MOA



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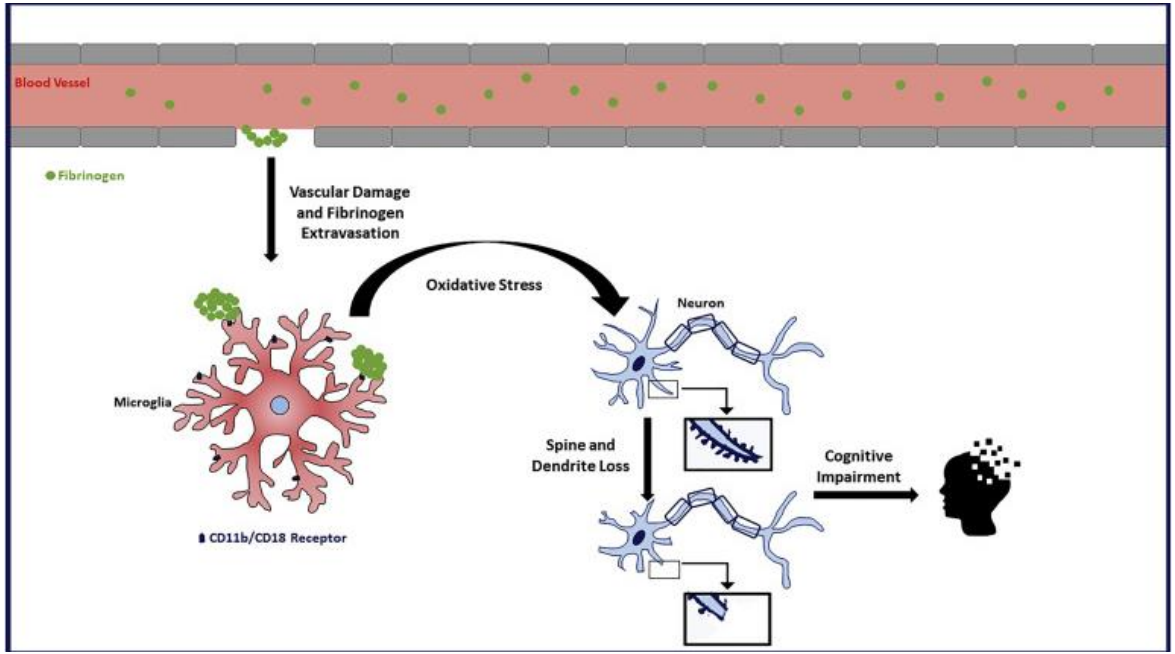
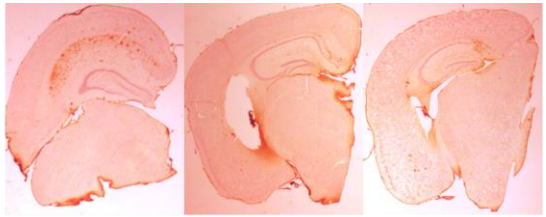
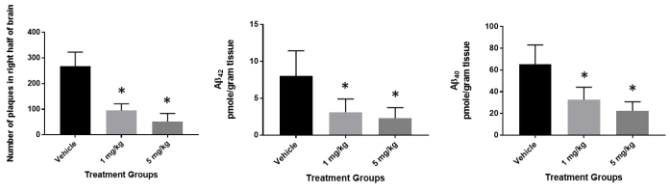


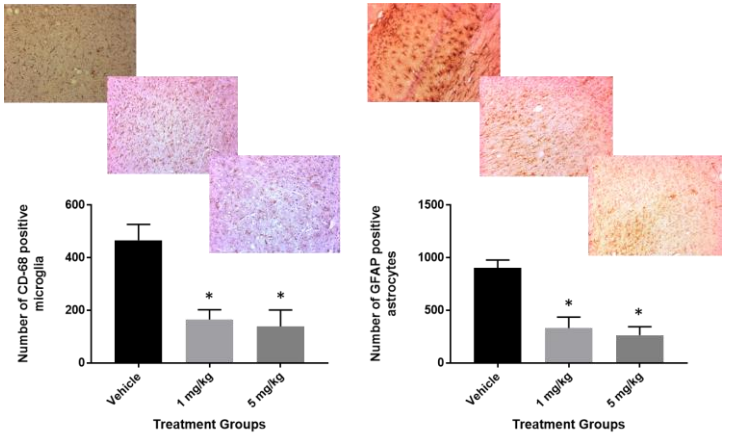
When There Is Damage to Blood Vessels of the Brain, as in AD, Fibrinogen Can Leak into the Parenchyma

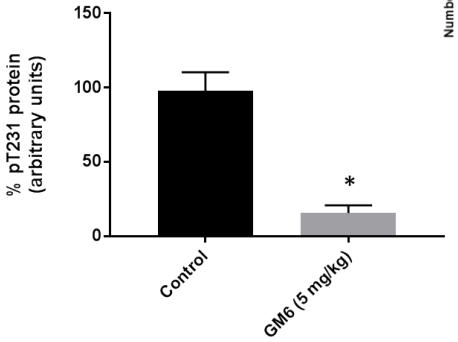
Ahn et al., 2019

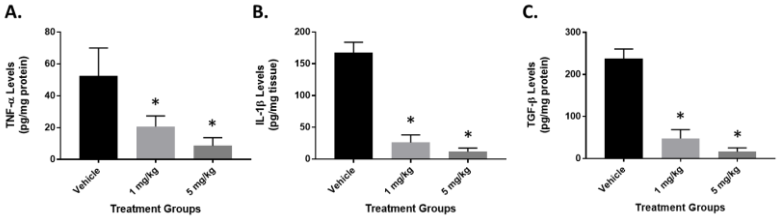
GM6 impacts Fibrinogen, inflammation, Aβ and tau

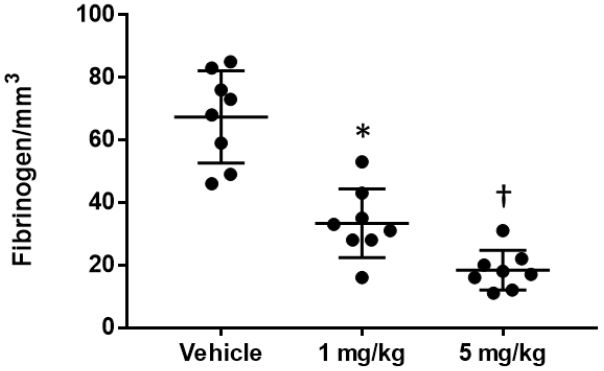












GM6 and Alzheimer's disease

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 fibrinogen (FBN) levels by ELISA in the brain of APP mice. 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 the APP mice, fibrinogen levels decreased by 75% in the brains, amyloid plaques decreased by 60%, and Nerve Growth Factor (NGF) increased by 600%. In both APP and h-tau mice, inflammation cytokines TNF-α, IL-1β, IL-6 and TGF-β were reduced by 80-90%. A similar pattern is observed in SOD1 mice model for ALS.

Conclusions

In conclusion, these findings suggest that GM6 may attenuate inflammation in Alzheimer's disease pathology via multiple pathways, including acting on fibrinogen which concurrently reduces Aβ peptide and phosphorylated tau. GM6 may be a feasible approach in the treatment of AD as a pleiotropic regulator which simultaneously acts upon multiple extracellular receptors to modulate a series of signaling pathways mediating inflammation, decreased Aβ toxicity and pro-survival responses.

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