In-Vivo Study on Nose-to-Brain Delivery of Liposomal siRNA/Drug Combination for Alzheimer's Disease

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Background

Despite decades of study, the primary therapeutic interventions for Alzheimer's Disease (AD) remain limited, with donepezil and memantine at the forefront of today's treatment regimen. Several challenges persist in devising more effective medicine options with the blood-brain-barrier (BBB), aggregation of amyloid beta (Aβ) protein in the brain, and the lack of potency/selectivity with orally/intravenously delivered small molecule-based approaches. To address these hurdles, our lab has designed a novel liposomal formulation that can be administered via the intranasal route, which is being increasingly recognized for its therapeutic potential in bypassing the BBB and delivering payloads with limited off-target effects. Herein, we have demonstrated the safety and efficacy of a triple-drug liposomal therapy comprised of BACE-1 siRNA, donepezil, and memantine administered to transgenic APP/PS1 mice.

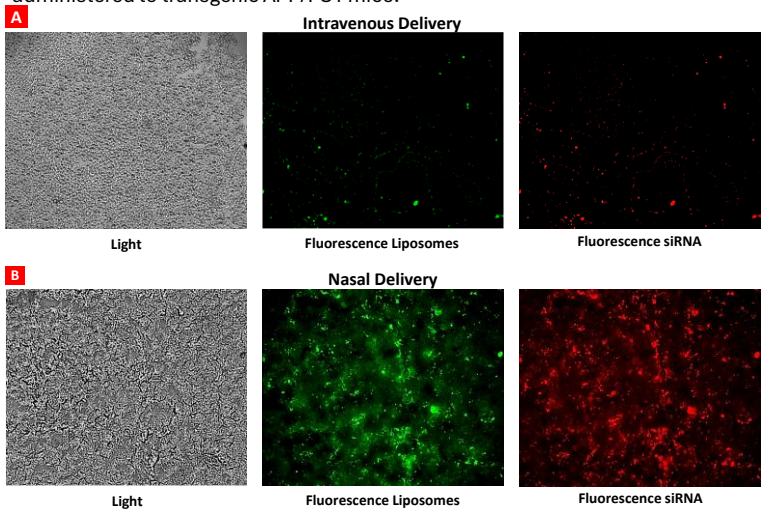

Figure 1. Accumulation of liposomes (green) and siRNA (red) in brain tissue after intravenous (A) and nasal (B) delivery. Confocal fluorescence microscope images of frozen 5 μm brain tissue sections.

Conclusions

Our findings showcase the increased potency, selectivity, and efficacy of administering a siRNA combination liposomal therapy via nose-to-brain delivery for the treatment of AD when compared to conventional approaches. Several key biomarkers associated with the onset/progression of AD were significantly reduced and phenotypic readouts suggest symptomatic improvement. This technology can be applied for the treatment of other neurological conditions, including brain cancer.

Methods

APP/PS1 homozygous, transgenic mice with C57BL/6; C3H genetic background, and wild-type (WT) mice were procured. Liposomal formulations were generated in-house utilizing a Rotary Evaporation method where donepezil, memantine, and BACE-1 siRNA were incorporated and characterized. Cohorts of mice were treated with separate routes of administrations, dosages, and drug formulations for a comprehensive analysis. Mice underwent Y-maze behavior tests, and brain tissue samples were collected for in-vitro biomarker evaluation. Nose-to-brain delivery was performed using a nasal catheter device.

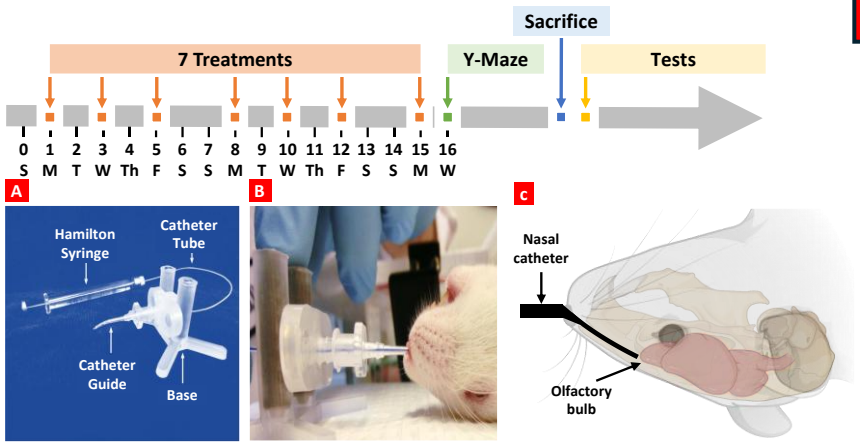

Figure 2. Schematic illustration of experimental timeline. (A) Intranasal catheter device. (B) Anesthetized animal in the supine position with catheter inserted to reach the olfactory region. (C) Schematic of catheter tube location before dosing.

Results

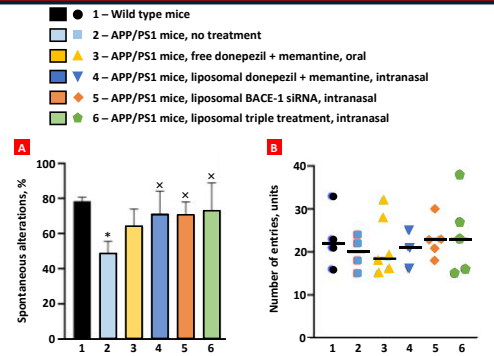

Figure 3. Spontaneous alternation (A) and number of arm entries (B) among the treatment groups in Y-maze test

Results (Cont'd)

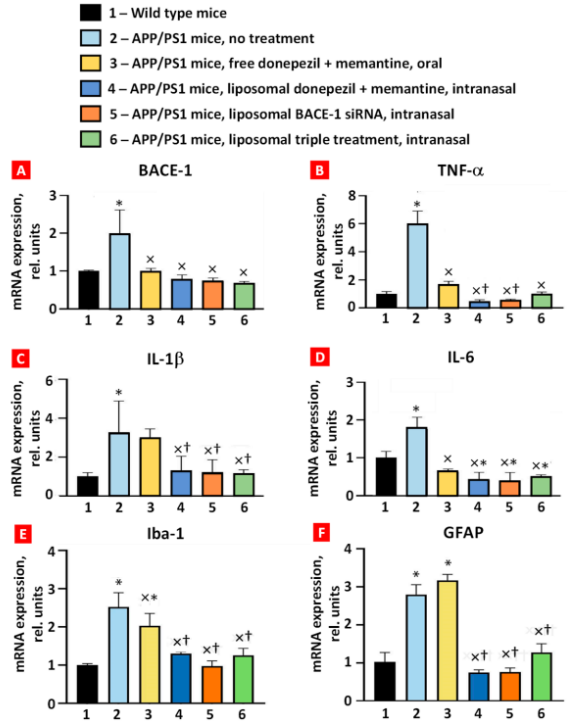

Figure 4. Expression of BACE-1 (A), TNF-α (B), IL-1β (C), IL-6 (D), Iba-1 (E), and GFAP (F) mRNAs in mouse brain tissues.

Nose-to-brain delivery yielded a more significant accumulation of liposomes confirmed through confocal fluorescent microscopy in brain tissue sections. Intranasal administration and triple combination liposomal therapy in conjunction demonstrated greater efficacy in decreasing BACE-1 activity and inflammatory cytokines (TNF-α, IL-6, IL-1β Iba-1, and GFAP). Mice treated with the liposomal combination therapy via intranasal route exhibited higher spontaneous alternation in the behavioral Y-maze test, suggesting enhanced short-term memory when compared to the untreated group.