

Abstract #12898: Intranasal Delivery Of Engineered Extracellular Vesicles With Bdnf-high Expression for Alzheimer's Disease Therapy

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Background

- Alzheimer's disease (AD) is a common neurodegenerative disorder characterized by progressive cognitive decline, and effective disease-modifying therapies remain lacking.
- Mesenchymal stem cell-derived small extracellular vesicles (MSC-sEVs) have shown therapeutic potential because of their favorable biocompatibility, low immunogenicity, and neuroprotective properties.
- Brain-derived neurotrophic factor (BDNF) is essential for synaptic plasticity, learning and memory, and neuronal survival, and is closely implicated in AD pathogenesis.
- This study investigated the therapeutic effects of BDNF-overexpressing sEVs (BDNF-sEVs) and their underlying mechanisms in APP/PS1 mice.

Methods

- Biodistribution & cellular uptake**
Intranasally delivered mCherry-labeled sEVs to APP/PS1 mice for detection of brain distribution and cellular internalization.
- Biosafety assessment**
Repeated intranasal injection of BDNF-sEVs; biosafety assessed via hematoxylin and eosin (H&E) staining.
- Cognitive function evaluation**
Performed novel object recognition, Y-maze, and Morris water maze tests. Assessed cognitive abilities using the novel object recognition test, Y-maze test, and Morris water maze test.
- Hippocampal pathological analysis**
Analyzed hippocampal lesions and related molecules by immunofluorescence, transmission electron microscopy, quantitative proteomics, and western blotting.

Results

- Biodistribution & cellular uptake:** Intranasally delivered sEVs entered the brain and accumulated in AD-vulnerable regions, including the hippocampus (**Fig. 1**), cortex, and olfactory bulb. Uptake was highest in hippocampal neurons, followed by microglia and astrocytes.
- Biosafety:** No obvious pathological abnormalities were detected in major peripheral organs or nasal mucosa after repeated administration.
- Cognitive improvement:** BDNF-sEV-treated APP/PS1 mice exhibited improved performance in the novel object recognition, Y-maze, and Morris water maze tests, with greater overall effects than unmodified sEVs.

Fig. 1: mCherry-labeled sEVs in hippocampal neurons.

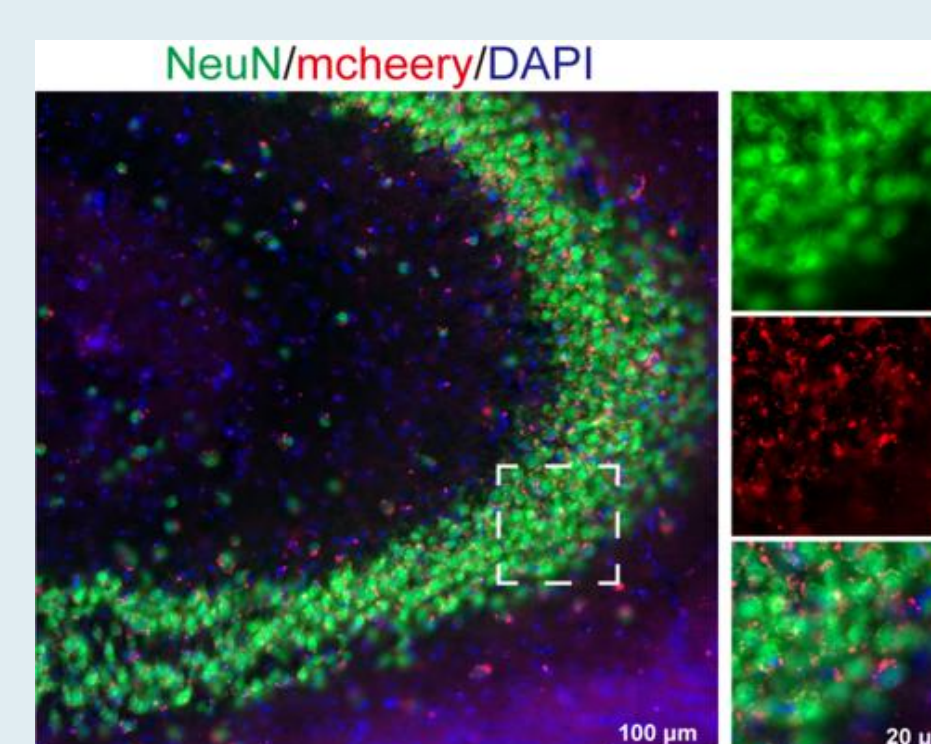
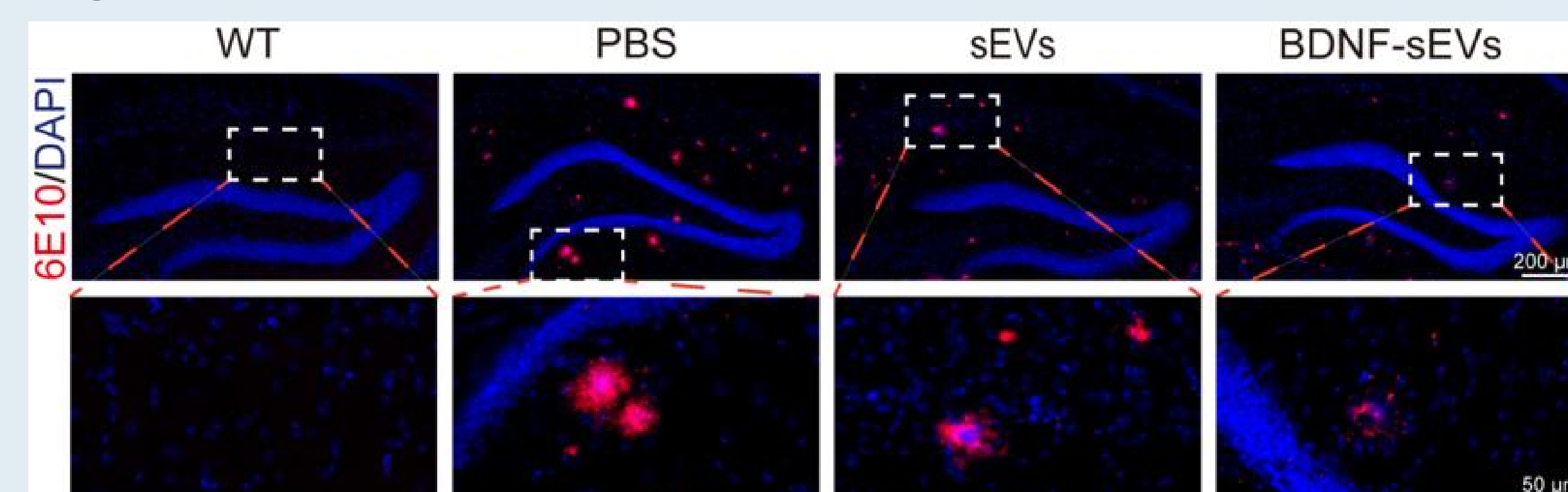
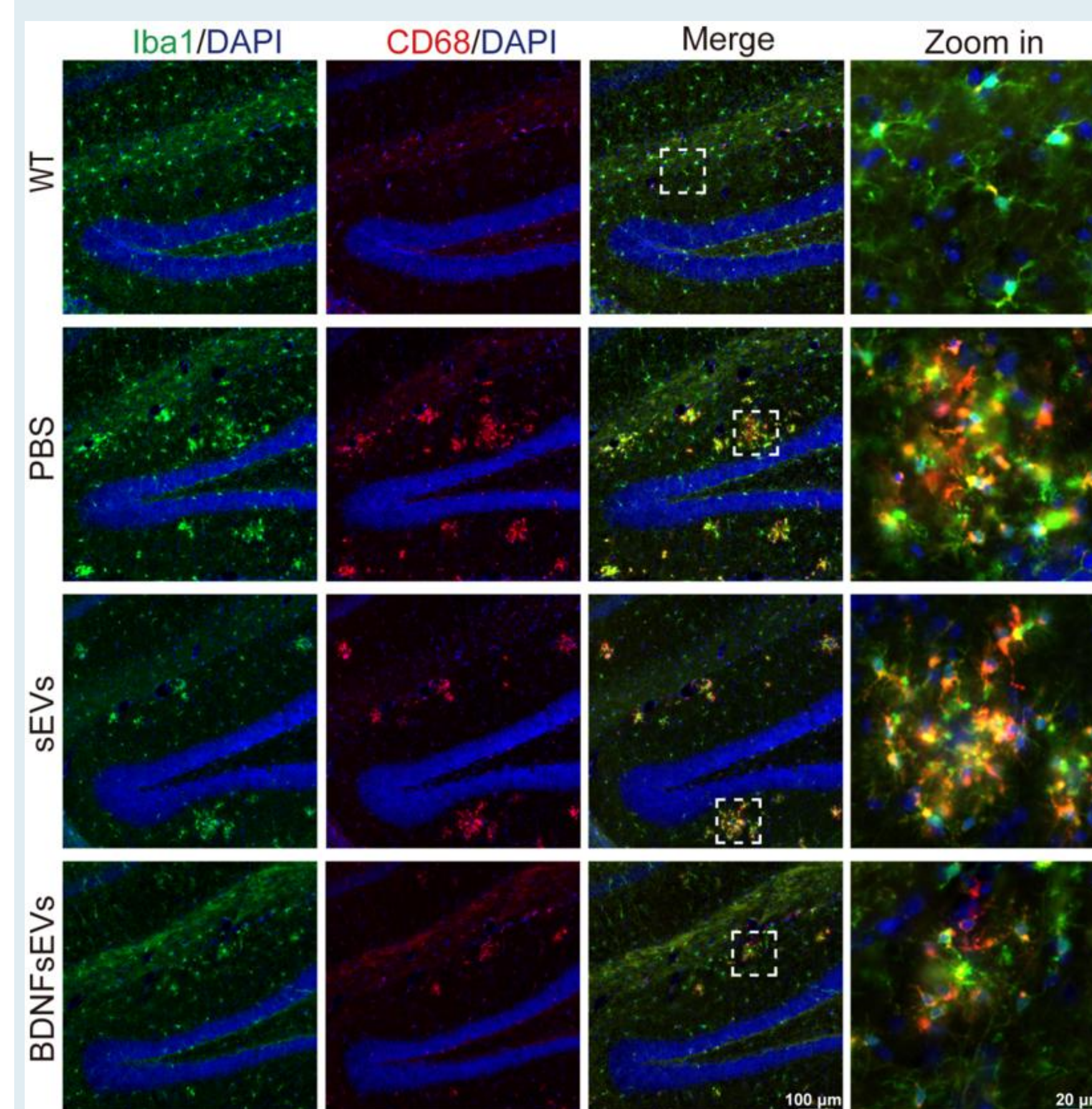


Fig. 2: BDNF-sEVs reduce Aβ deposition.



- Histopathological changes:** BDNF-sEV treatment reduced hippocampal Aβ burden (**Fig. 2**), increased NeuN-positive neuronal density in the dentate hilus, attenuated microglial activation (**Fig. 3**), and restored AQP4 polarization.
- Ultrastructural alterations:** Hippocampal synaptic density increased, and mitochondrial damage was alleviated after BDNF-sEV treatment.
- Proteomic profiling:** BDNF-sEVs partially ameliorated AD-associated protein dysregulation, with enrichment of lipid metabolism-related pathways, including PPAR signaling, as well as neuroactive ligand-receptor interaction pathways.
- Molecular mechanism:** Hippocampal BDNF level was elevated, accompanied by increased phosphorylation of TrkB, Akt, Erk and PLCγ1.

Fig. 3: BDNF-sEVs attenuate microglial activation.



Conclusion

Intranasal BDNF-sEV delivery showed favorable brain delivery efficiency and biosafety, improved cognitive deficits and AD-related pathology in APP/PS1 mice, and may exert these effects through activation of BDNF/TrkB downstream signaling and partial correction of AD-associated proteomic abnormalities.