Therapeutic Potential of INM-901 in Mitigating Alzheimer's Disease Pathology: Insights from a Long-term 5xFAD Mouse Model Study

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INTRODUCTION

Alzheimer's Disease (AD) impacts 6.9+ million people in the US; costs exceed $700B/year.

Existing treatments offer only symptomatic relief with limited impact on disease progression and no cure. Amyloid-beta (Aβ) antibody therapies have limitations: low efficacy, side effects, and high cost.

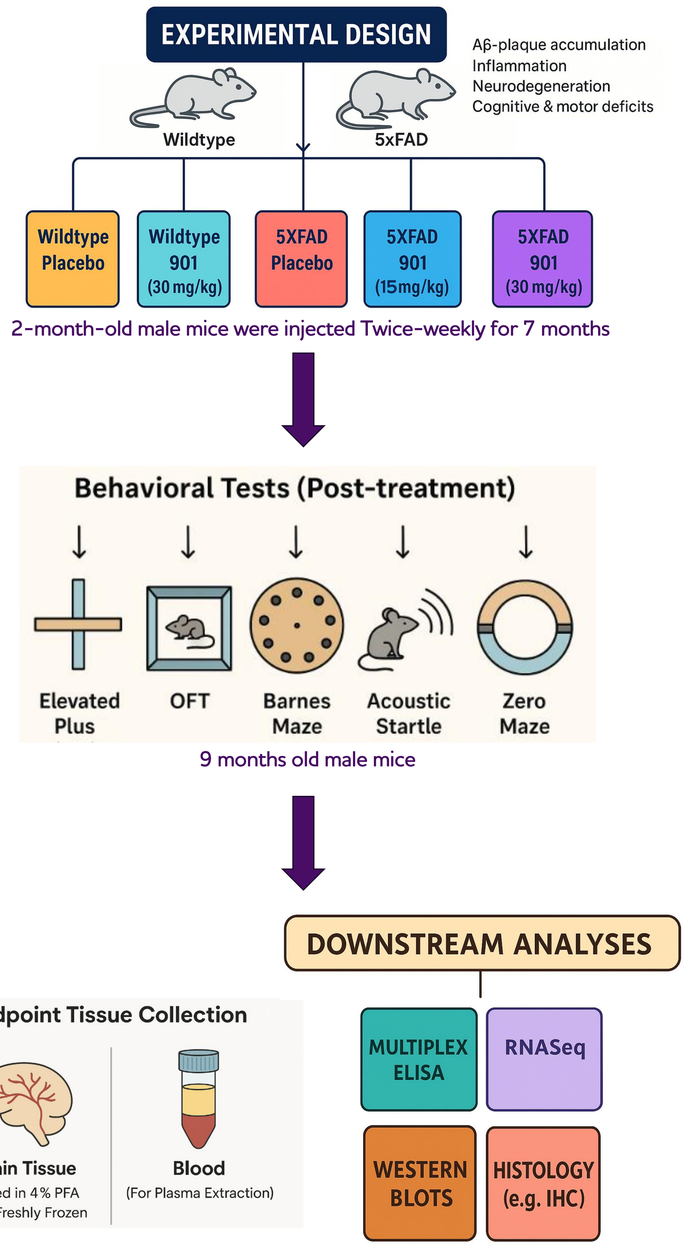
There is a critical need to identify compounds that go beyond symptom management and target underlying disease mechanisms.

Cannabinoids have demonstrated neuroprotective potential in AD by acting through their cognate receptors, CB1R and CB2R, to reduce Aβ toxicity, neuroinflammatory responses and cognitive decline - key pathological features of AD - thereby holding promise in improving brain function.

This study evaluates INM-901*, a novel synthetic cannabinoid analog in the 5xFAD AD mouse model, using a longer treatment duration and a more advanced disease stage to validate and expand upon previous findings.

*INM-901 is a proprietary cannabinoid analog.

METHODS



RESULTS

Behavioral Studies

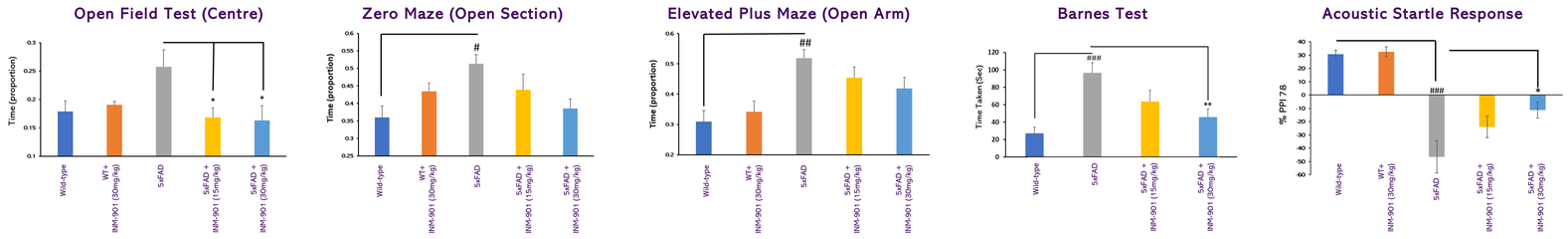


Fig 1: Behavioral Differences in Anxiety, Cognition and Sensory Response Among Wild-type, 5xFAD, and INM-901-Treated 5xFAD Mice

OFT, Zero Maze, and EPM: 5xFAD mice spent more time in the center zone or open arms, suggesting reduced anxiety-like behaviour; INM-901 treatment restored typical anxiety-like behaviour similar to Wild-type mice. **Barnes Maze:** 5xFAD mice showed impaired spatial learning and memory, while INM-901 treatment improved performance, approaching Wild-type levels. **Acoustics Startle Response:** 5xFAD mice showed reduced acoustic startle response compared to Wild-type mice, indicating sensory dysfunction, which was partially restored by INM-901 treatment. (A one-way ANOVA was conducted to compare means among groups, followed by Tukey's post-hoc analysis. # compared to Wild-type; * compared to 5XFAD; n=9-14)

Inflammatory Markers

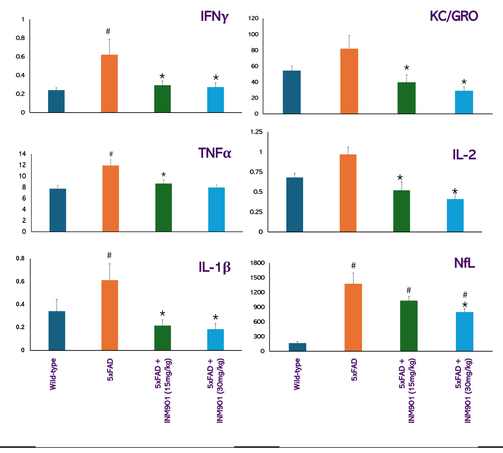


Fig 2: Multiplex analysis using Meso Scale Discovery (MSD) technology to quantify levels of IFN-γ, TNF-α, IL-1β, KC-GRO, IL-2 and NfL levels. 5xFAD transgenic mice exhibited significantly elevated levels of these markers compared to Wild-type mice. Treatment with INM-901 at 15 and/or 30 mg/kg resulted in a significant reduction in these biomarkers, suggesting a dose-dependent therapeutic effect of INM-901 in the 5xFAD AD model. A one-way ANOVA was conducted to compare means among four groups, followed by Tukey's post-hoc analysis. # compared to WT ; * compared to 5XFAD; n=10-14

Hippocampal RNA Expression

Cytokines- Inflammation

Genes	5xFAD vs Wild-Type	5xFAD vs INM-901 (15 mg/kg)	5xFAD vs INM-901 (30 mg/kg)
Trem2	↑↑↑	↓↓	↓
GFAP	↑↑	↓	↓↓
TLR2	↑↑	-	↓↓
CD33	↑	↑	↓
Cx3Cl1	↑↑	↓	-

ECS Related Genes

Genes	5xFAD vs Wild-Type	5xFAD vs INM-901 (15 mg/kg)	5xFAD vs INM-901 (30 mg/kg)
DAGLα	↓↓	↑	↑↑
DAGLβ	-	↑	↑↑
NAPE-PLD	↓↓	↑	-
CNR1	↓↓↓	↑	↑↑
CNR2	↑↑↑	↓↓↓	↓↓

Synaptic Dysfunction

Genes	5xFAD vs Wild-Type	5xFAD vs INM-901 (15 mg/kg)	5xFAD vs INM-901 (30 mg/kg)
Camk2a	↓↓	↑	-
Grin2a	↓↓↓	↑↑↑	↑↑
Alph1b	↑↑↑	↓	↓↓
Nrxn1	↓↓	-	↑
Mink1	↓↓	↑↑	↑↑↑
Cacna1a	↓↓	↑↑	↑↑↑

Oxidative Stress and Cell Death

Genes	5xFAD vs Wild-Type	5xFAD vs INM-901 (15 mg/kg)	5xFAD vs INM-901 (30 mg/kg)
SOD1	↑↑↑	↓↓↓	↓↓
GPX1	↑↑↑	↓↓↓	↓↓
NFE2L2	↑↑↑	↓↓	↓↓↓
CASP3	↑↑	↓↓↓	↓↓
APOE	↑↑	↓↓	↓↓↓
SORL1	↓	↑	↑

Fig 3: Data illustrates changes in hippocampal RNA expression for genes-associated with (1) inflammation, (2) ECS, (3) synaptic dysfunction, and (4) oxidative stress and apoptosis. The heatmap displays $\log_2$-fold changes in gene expression obtained from RNA-seq analysis, comparing experimental groups to relevant controls (e.g., 5xFAD vs. Wild-Type, and 5xFAD treated with 15 mg/kg or 30 mg/kg INM-901 vs. placebo-treated 5xFAD mice). Gene expression changes are represented using directional arrows to indicate transcript-level changes: (↑) Upregulated; (↓) Downregulated; (-) No Change (n=10-14)

Immunohistochemistry

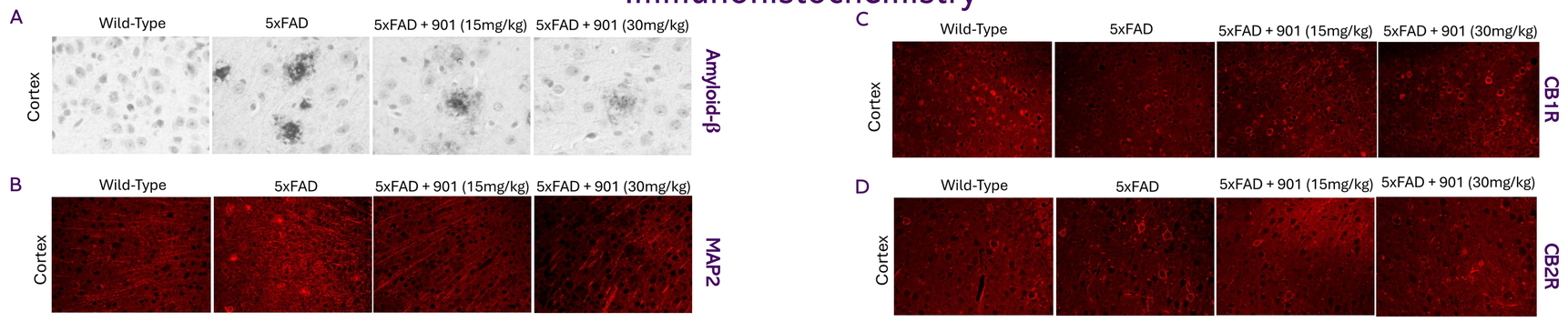
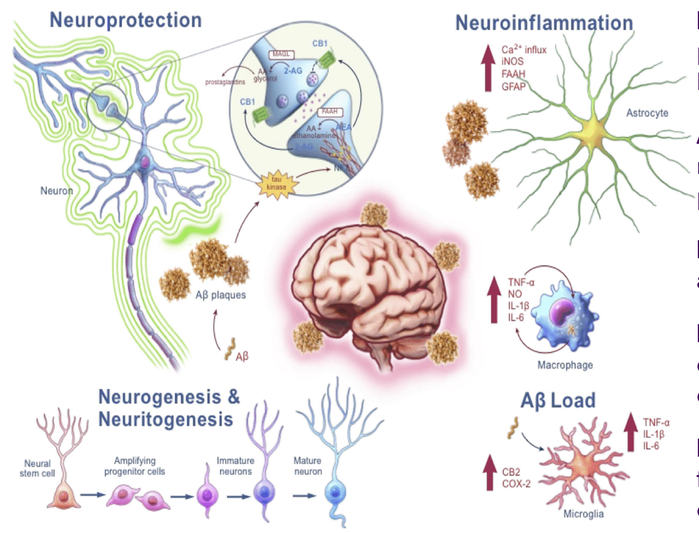


Fig 4: Representative immunohistochemical photomicrographs of cortical sections (400× magnification) from Wild-type, 5xFAD, and 5xFAD mice treated with INM-901 (15 mg/kg and 30 mg/kg).
(A) Amyloid-β (Aβ) immunoreactivity is markedly elevated in 5xFAD mice relative to wild-type and is attenuated following INM-901 administration in a dose-dependent manner. (B) MAP2, a dendritic marker, shows reduced expression and disrupted morphology in 5xFAD cortex, which is partially restored with INM-901 treatment. (C) CB1R expression is diminished in 5xFAD mice and exhibits increased immunoreactivity upon INM-901 treatment. (D) CB2R levels are elevated in 5xFAD mice and reduced toward baseline following INM-901 treatment at both doses.

CONCLUSIONS



Behavioral Improvements: INM-901 demonstrates positive trends in cognitive function, anxiety-related behavior, and sensory responsiveness.

Anti-Inflammatory Action: INM-901 demonstrates strong neuroinflammatory modulation in Alzheimer's pathology.

Neuroprotection: INM-901 significantly reduces amyloid-beta-induced cell death.

Neuronal Regeneration: INM-901 promotes neurite outgrowth, indicating its ability to enhance neuronal connectivity and function.

Molecular Validation: mRNA data aligns with behavioral findings, supporting observed improvements in cognition, memory and neurogenesis.

FUNDING

NSERC CRSNG

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