

Behavioral And Neurochemical Abnormalities
In Humanized Tau-FAD Combination Mice

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Kumar Sambamurti, Piyush Padhi, Manikandan G. Samidurai, Miguel A. Pappolla, Debomoy K. Lahiri, Nigel H. Greig, Sumit Sarkar, Gregory J. Phillips, Anumantha G. Kanthasamy. Medical University of South Carolina, University of Georgia, University of Texas, Indiana University School of Medicine, National Institute on Aging, Food and Drug Administration.

Combining human genomic Tau (MAPT) with 5xFAD (APP/PSEN1) in a mouse Mapt-null background produces measurable behavioral and neurochemical deficits. However, this model does not exhibit the robust accumulation of Tau into neurofibrillary tangles typically observed in human Alzheimer’s disease.

INTRODUCTION

RESULTS

KEY TAKEAWAYS

Familial Alzheimer’s disease (FAD) models expressing mutant *APP* and *PSEN1* have been invaluable for defining Aβ-dependent pathology; however, most do not allow separation of Aβ- and Tau-dependent effects due to tightly linked transgenes. To address this limitation, we generated HTAP mice by crossing hTau (JAX #005491), which expresses human wild-type *MAPT* and lacks mouse *Mapt*, with 5xFAD mice, and subsequently corrected the background for age-related hearing loss (HTAP2). This model enables parallel and independent evaluation of human Tau– and Aβ-driven mechanisms on a defined C57BL/6J background.

HTAP2 further provides a translational platform to study combined AD pathology and regulatory mechanisms, including microRNA-mediated control of *MAPT* via its 3’UTR alongside *APP*, as well as therapeutic strategies targeting neuroimmune and monoaminergic pathways.

To modulate monoaminergic deficits, *E. coli* Nissle (EcN^{rha}_{LD-H3}ΔTyrR) engineered to express 4-hydroxyphenylacetate 3-monooxygenase (HpaB/HpaC) was administered orally (1×10¹⁰ CFU) with benserazide (40 mg/kg). Plasma L-DOPA and 3-O-methyldopa (3-OMD) levels were quantified over 16 hours by HPLC.

Figure 1. Expression of amyloid and Tau in HTAP mice. Panel A shows Tau and phosphorylated Tau (pTau) in a Mapt-knockout mouse brain (n = 3). Panel B shows Amylo-Glo staining of Aβ plaques in the hippocampi of APP/PS1 and HTAP mice. Panel C shows pTau-T181 staining in hTau and HTAP mice.

IBA1/6E10/Hoechst CA1 region

Control

HTAP 2

Figure 2. Expression of amyloid and the microglial marker IBA1 in HTAP mice. Labeled panels show IBA1 immunostaining for microglia and 6E10 staining for Aβ in the CA1 region. Additional regions, including CA3, amygdala, and dentate gyrus, were also evaluated but are not shown.

Figure 3. Memory deficits in HTAP mice. All groups—5xFAD (FAD), hTau, wild type, and young HTAP (HTAP-Y)—rapidly learned the Barnes maze, whereas older HTAP mice exhibited impaired learning (left). The right panel shows a scatter plot of the mean of the final three time points, illustrating group sizes and variability in escape latency.

Figure 4. Reduced norepinephrine (NE) levels in HTAP mice across brain regions. HTAP mice (n = 13) and wild-type C57BL/6J mice (n = 6), including both sexes, were microdissected. The hippocampus (Hip), frontal cortex (FC), and striatum (Str) were analyzed for NE levels by HPLC

Figure 5. Single Dose - EcN^{rha}_{LD-H3}ΔTyrR Pilot Study Design

4 Groups (n = 6)
Group 1: 0, 5, 2, 8 h
Group 2: 1, 6, 12h
Group 3: 4, 16, 24h
Group 4: 36, 48h

EcN^{rha}_{LD-H3}ΔTyrR (1 × 10¹⁰) p.o.
Benserazide (40mg/kg) p.o.

Plasma Collection
1H Stool Collection

Baseline
0.5 1 2 4 6 8 12 16 24 36 48 Hours

HTAP
n = 6/timepoint

Terminal Brain Collection

PP-0126 = EcN^{rha}_{LD-H3}ΔTyrR

Figure 6. Plasma L-DOPA and its key metabolite. A single dose of EcN^{rha}_{LD-H3}ΔTyrR in HTAP mice shows moderate stability for up to 4 hours; however, substantial peripheral conversion to 3-O-methyldopa (3-OMD) occurs via catechol-O-methyltransferase (COMT). Future studies will incorporate the COMT inhibitor entacapone to reduce this conversion and improve the therapeutic efficacy of L-DOPA (n = 6).

The HTAP2 mouse model combines AD pathology by integrating human *MAPT* with FAD mutations and exhibits behavioral and catecholaminergic deficits.

Engineered *E. coli* Nissle enables sustained in vivo L-DOPA production, providing continuous 6–8 h delivery and avoiding pharmacokinetic peaks of standard therapy.

Restores monoaminergic deficits and is well tolerated, supporting a promising, translational microbial-based therapeutic strategy under active investigation.

sambak@musc.edu

Anumantha.Kanthasamy@uga.edu

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