

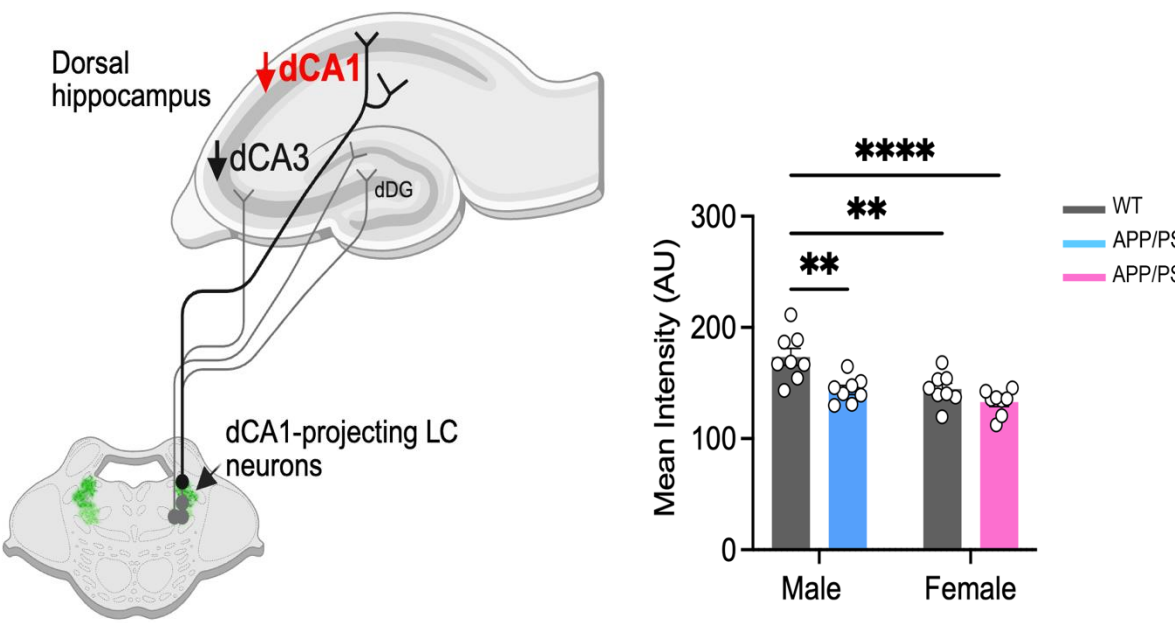
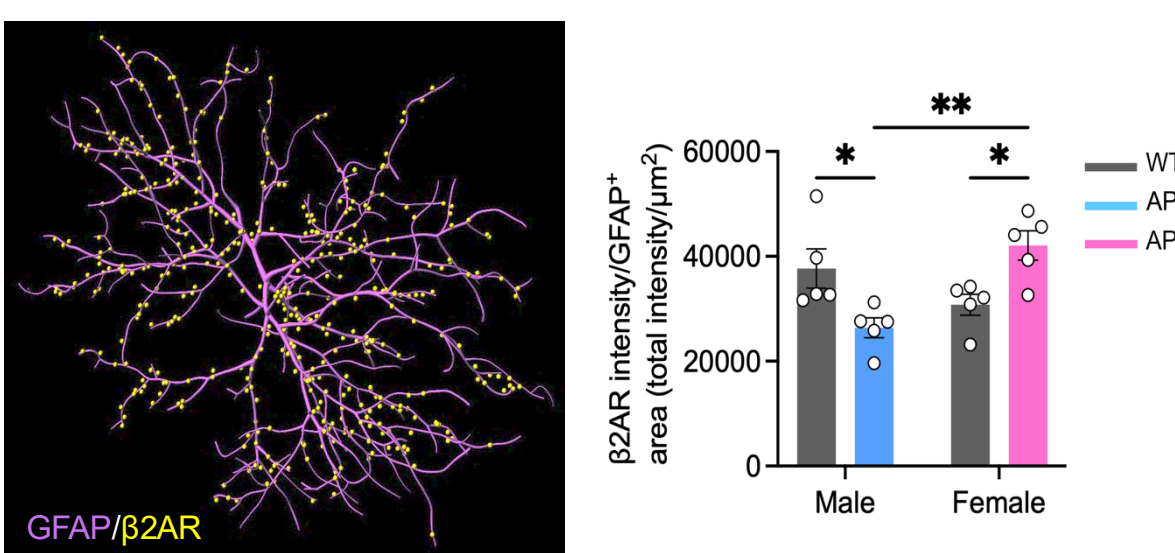
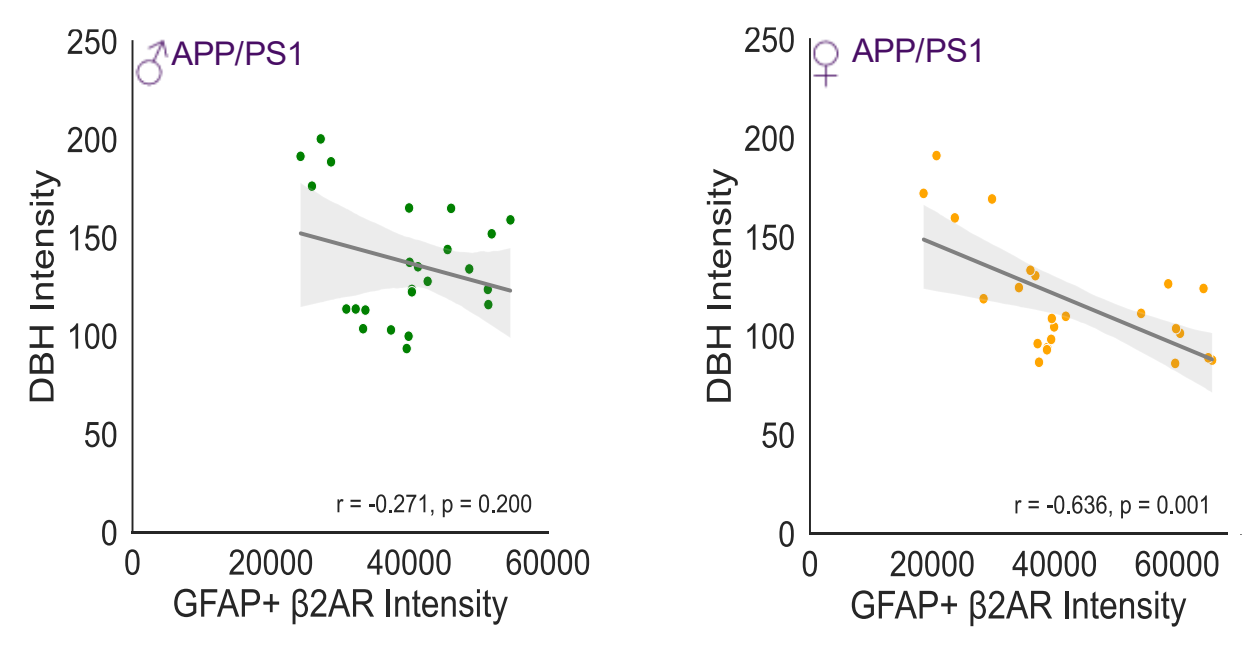
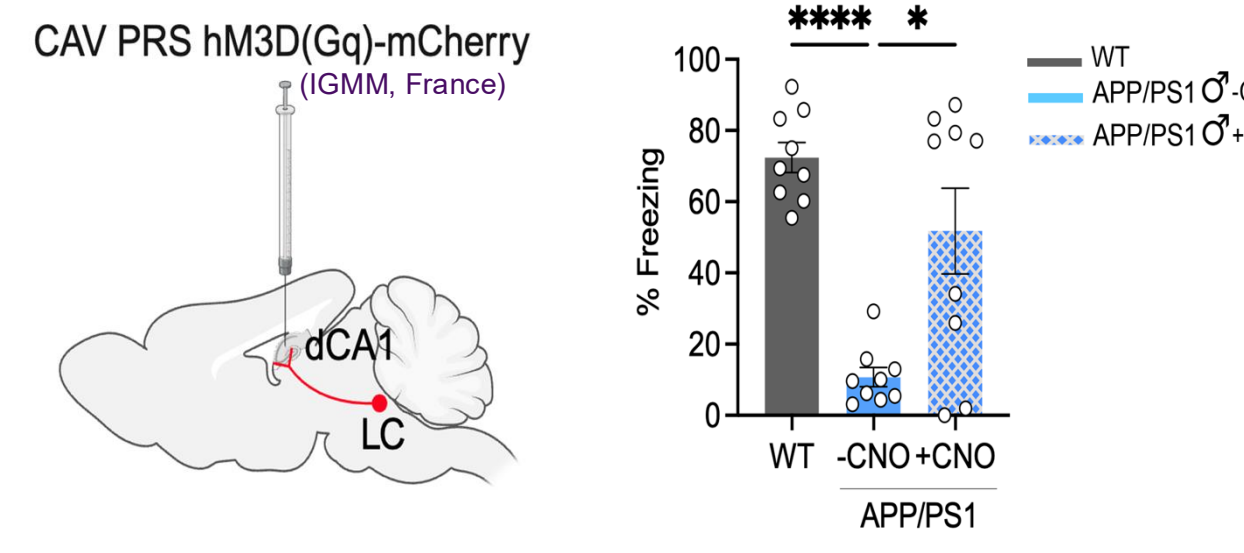
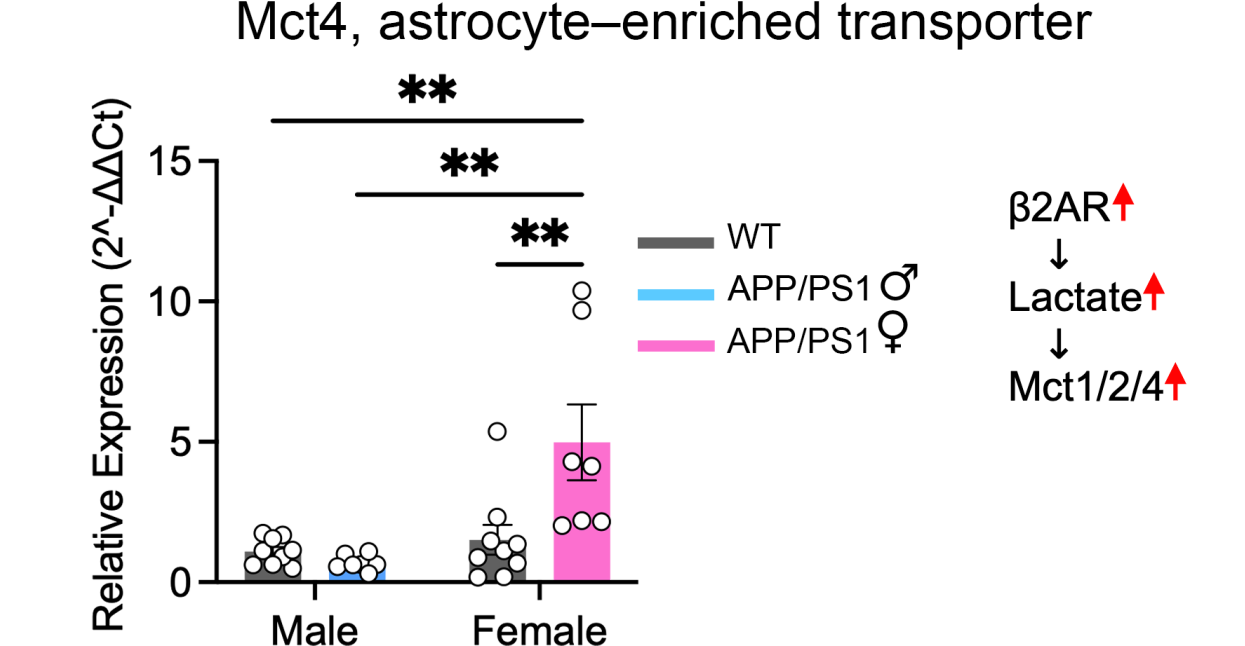
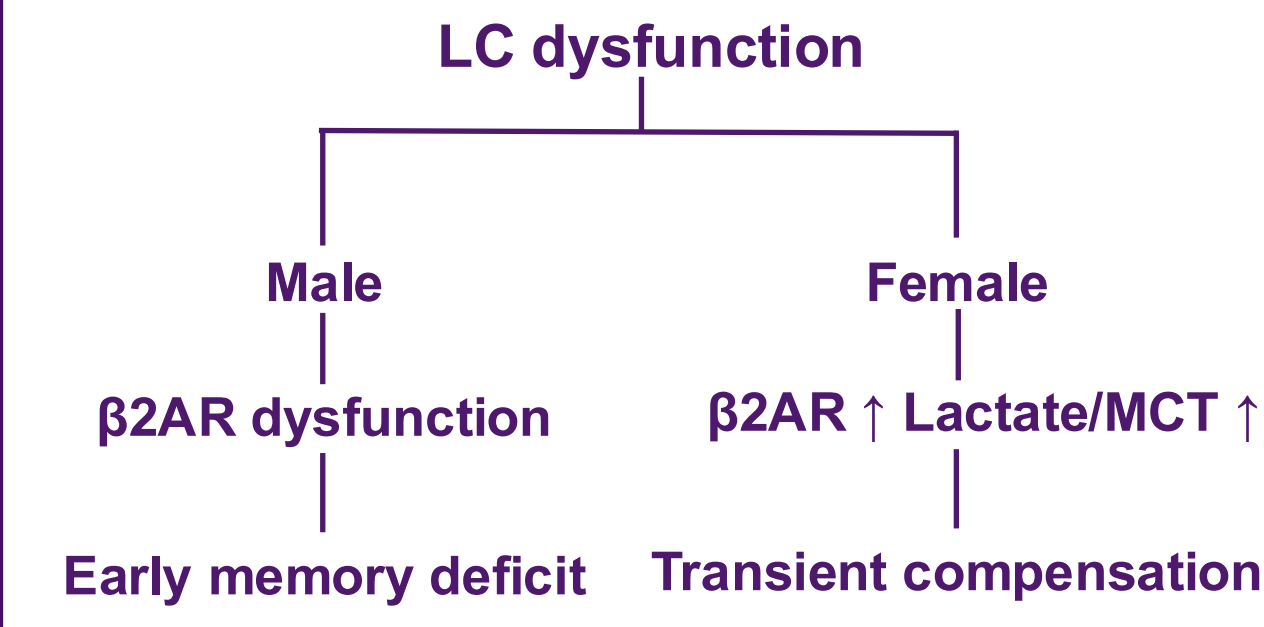
Sex-specific astrocytic β 2-adrenergic signaling contributes to early locus coeruleus–hippocampal dysfunction in APP/PS1 mice



Rupsa Roy Choudhury^{1,2}, Srishti Kushwaha^{1,2}, Smitha Karunakaran¹

¹Centre for Brain Research, Indian Institute of Science, Bangalore, India | ²Manipal Academy of Higher Education, Manipal, India

Early LC–hippocampal dysfunction in APP/PS1 mice is sex-divergent: **males** show noradrenergic terminal loss, disrupted astrocytic β 2AR–metabolic coupling and early memory failure, whereas **females** recruit astrocytic β 2AR–lactate/MCT support that transiently preserves memory precision.

INTRODUCTION		RESULTS		WORKING MODEL				
Background: The locus coeruleus is among the earliest regions affected in Alzheimer's disease. Astrocytic β2AR signalling regulates astrocyte–neuron metabolic interactions important for hippocampal function. Study Aim: Determine whether early LC dysfunction engages distinct astrocytic β2AR–lactate/MCT mechanisms in male and female APP/PS1 mice.		1. Selective LC terminal loss  Region-specific DBH⁺ terminal loss occurs in the dorsal hippocampus, whereas females preserve terminal density through structural remodeling. 2. Female-specific β2AR remodeling  Females upregulate astrocytic β2AR, whereas males show blunted β2AR responses.		3. Astrocytic β2AR supports preserved memory  Higher astrocytic β2AR expression correlates with better contextual fear memory in females. 4. LC activation restores hippocampal function  Acute LC activation rescues early contextual memory deficits in male APP/PS1 mice.		5. Metabolic compensation delays female vulnerability  Females recruit β2AR–lactate/MCT metabolic support before progressive memory decline.		 REFERENCES Related publication <i>Kushwaha S, Roy Choudhury R*, et al. Alzheimer's & Dementia (2026)</i> 
METHODS		CONCLUSIONS		FUNDING				
APP/PS1 and WT mice Male & female, early pre-plaque stage ↓ LC–hippocampal terminals DBH⁺ density and morphology ↓ Astrocytic β2AR signaling GFAP-associated β2AR (2D & 3D) ↓ Memory & circuit function Contextual fear memory • LC DREADD activation ↓ Metabolic coupling Lactate • MCT1 • MCT2 • MCT4		✓ Early LC dysfunction is sex-specific. ✓ Male APP/PS1: disrupted β2AR–metabolic coupling. ✓ Female APP/PS1: compensatory β2AR–lactate support ✓ Astrocytic β2AR signalling is an early substrate of resilience.		Centre for Brain Research (CBR), IISc Pratiksha Trust				
				 smitha@cbr-iisc.ac.in 				