

Molecular interplay between human IAPP and tau pathology in a double-transgenic mouse model of type 2 diabetes and tauopathy

Inés López del Castillo^{1,2}, Maria Angeles Arredondo-Alcala^{1,2}, Jesus Garcia-Martin^{1,2}, Antonia Gutierrez^{1,2}, Ines Moreno-Gonzalez^{1,2,3}.

1- Departamento de Biología Celular, Fisiología y Genética, Facultad de Ciencias, Universidad de Málaga, Instituto de Investigación Biomédica de Málaga y Plataforma en Nanomedicina-IBIMA Plataforma BIONAND, Málaga, Spain. 2- Centro de Investigación Biomédica en Red (CIBER), Madrid, Spain. 3-Department of Neurology, McGovern Medical School, UTHealth Houston, Houston, TX, USA.



Background

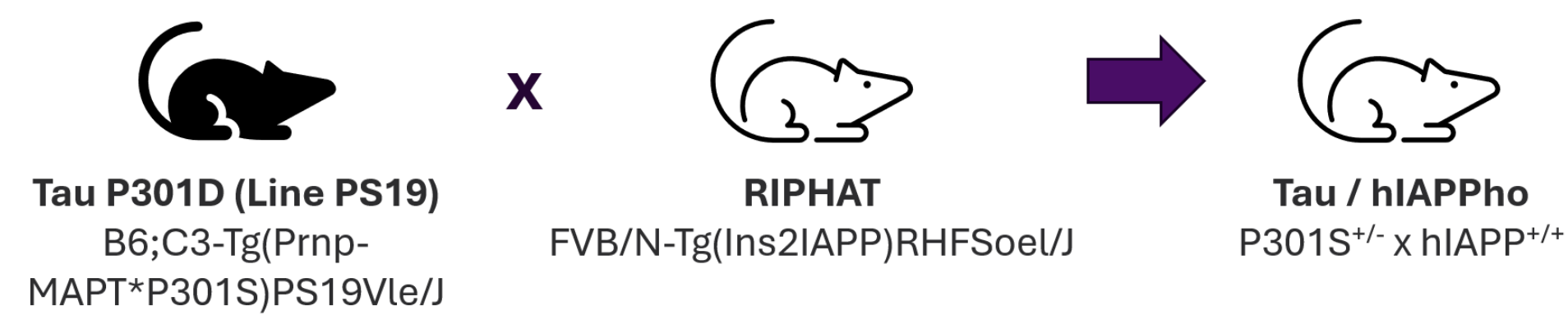
Type 2 diabetes (T2D) is a significant risk factor for Alzheimer’s disease (AD), being both conditions proteinopathies. In T2D islet amyloid polypeptide (IAPP), also known as amylin, misfolds and aggregates in pancreatic islets forming amyloid depositions and finally leading to β -cell death. Interestingly, A β and hyperphosphorylated tau (ptau) – the major histopathologic hallmarks present in the brain of AD patients – have been identified together with IAPP in pancreatic islets from T2D individuals. IAPP has also been reported within A β plaques. Although human IAPP (hIAPP) is known to induce and accelerate A β aggregation *in vivo*, the molecular interplay between hIAPP and tau, and how it influences disease progression remain poorly understood.

Objective

To elucidate protein cross-talk between hIAPP and tau *in vivo* through the generation and characterization of a novel double transgenic mouse model.

Methods

• Generation of double transgenic mice:



Littermates (*tau*, *hIAPPPho*, *WT*) and a streptozotocin-injected *tau* control (*tau* + STZ; 2 x 110 mg/kg doses, 1 month pre-sacrifice) were used. Long-term survival was monitored for all groups.

- **Glucose tolerance test (GTT):** Prior to sacrifice, animals underwent an intraperitoneal GTT (2 g/kg) after 16 h fast.
- **Immunohistochemistry (IHC):** Neurofibrillary pathology and neuroinflammation were assessed in hippocampal sections through IHC for AT8 (ptau S202, T205 and S208), Iba1 (microglia) and GFAP (astrocytes).
- **Data analysis:** Image and statistical analyses were performed through FIJI and GraphPad Prism software, respectively.

Results

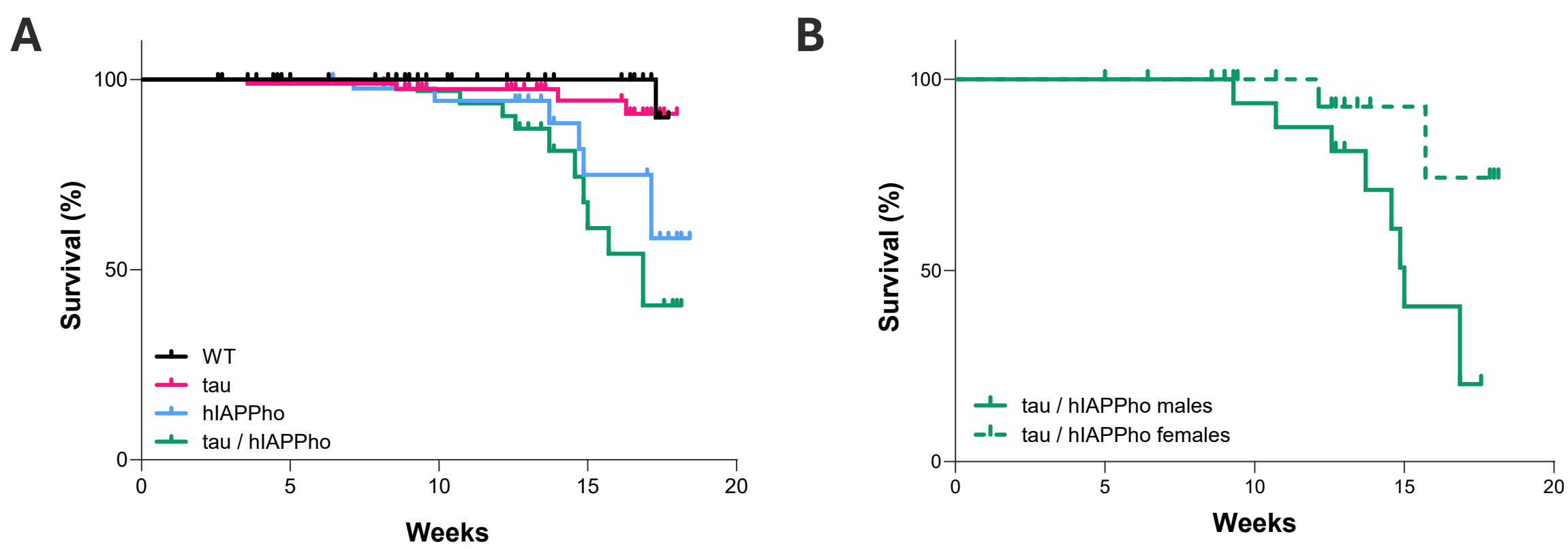


Figure 1. Synergistic effect of tau and hIAPP on animal survival showing marked sex dimorphism. **A.** Kaplan-Meier survival curves showing reduced longevity for the tau/hIAPPPho group (n = 44, median survival = 16.86 weeks) compared to controls (n = 44-91, survival > 50%). Log-rank (Mantel-Cox) test ($\chi^2 = 24.77$, df = 3, P < 0.0001); linear trend test ($\chi^2 = 22.63$, df = 1, P < 0.0001). **B.** Survival curves showing reduced lifespan in tau/hIAPPPho males (n = 23, median survival = 15 weeks) compared to females (n = 21; undefined median survival). Log-rank (Mantel-Cox) test ($\chi^2 = 4.313$, df = 1, P = 0.0378).

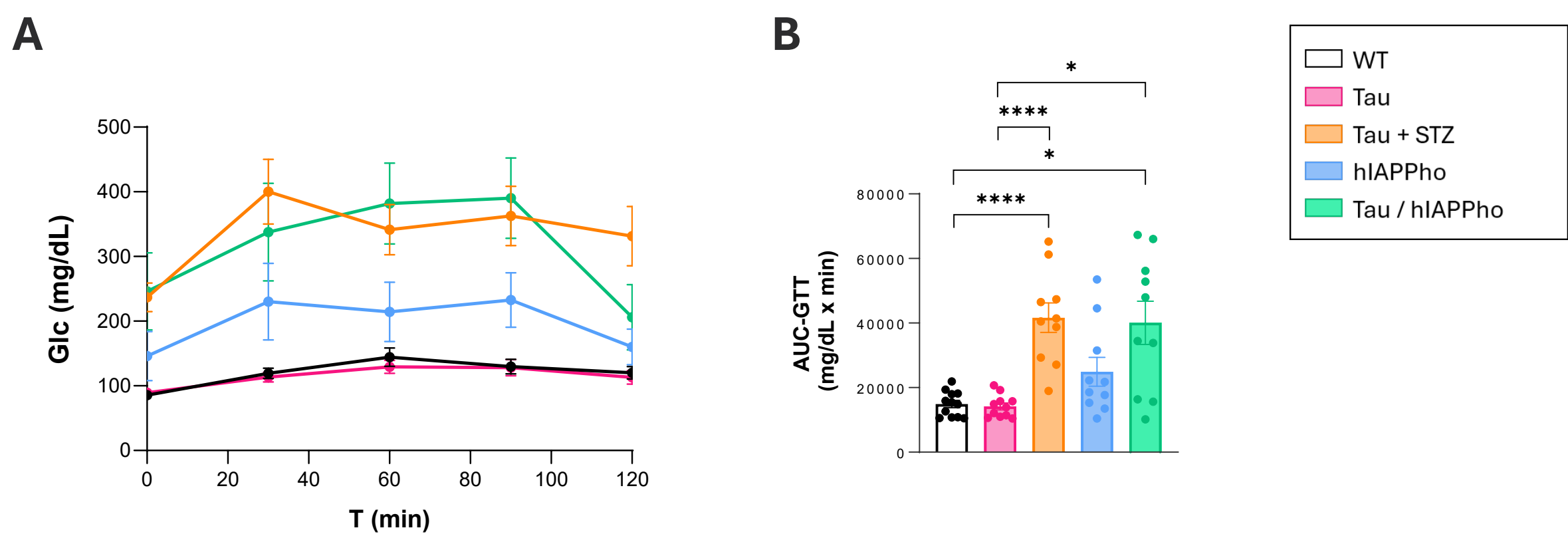


Figure 2. Tau diabetic models show impaired glucose homeostasis in 2-month-old mice. Results from glucose tolerance test (GTT). **A.** Blood glucose profile over 120 min. Mean $\pm$ SEM (n=10-12). Analyzed through a mixed-effects model: Genotype effect ($F_{4,48} = 11.10$, p < 0.0001); Time x Genotype interaction ($F_{16,192} = 2.34$, p = 0.0034). **B.** Area under the curve (AUC) in mg/dL x min. Mean $\pm$ SEM (n = 10-12). AUC data were log-transformed to achieve normality (Shapiro-Wilk) and analyzed by one-way ANOVA ($F_{4,28.78} = 12.15$, p < 0.0001) followed by Holm-Šidák post-hoc: *p < 0.05, ****p < 0.0001.

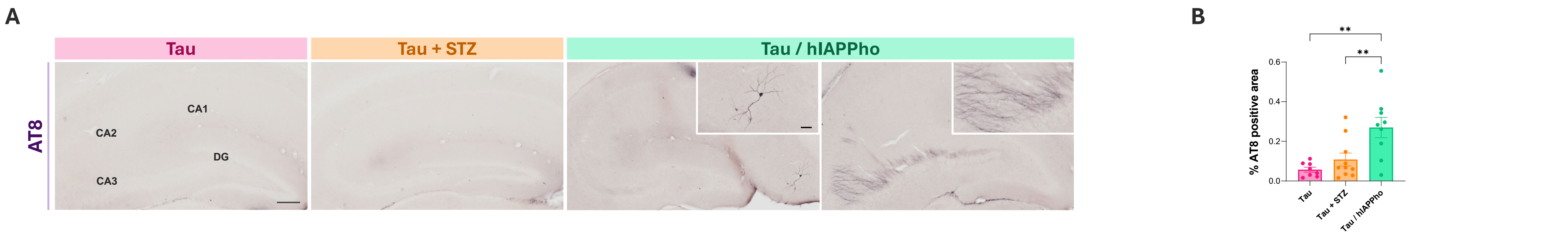


Figure 3. Double transgenic tau/hIAPPPho 2-month-old mice show early ptau pathology. **A.** Representative hippocampal IHC micrographs for AT8. The insets on tau/hIAPPPho images display details of cellular morphology and neurofibrillary pathology. DG: *Dentate Gyrus*; CA: *Cornu Ammonis*. Scale bar: main images, 200 μ m; detail insets, 80 μ m. **B.** Quantification of % AT8-positive area in the hippocampus. Data are presented as mean $\pm$ SEM. Statistics: One-way ANOVA ($F_{2,24} = 8.83$, p < 0.01), followed by Dunn’s post-hoc test (**p<0.01).

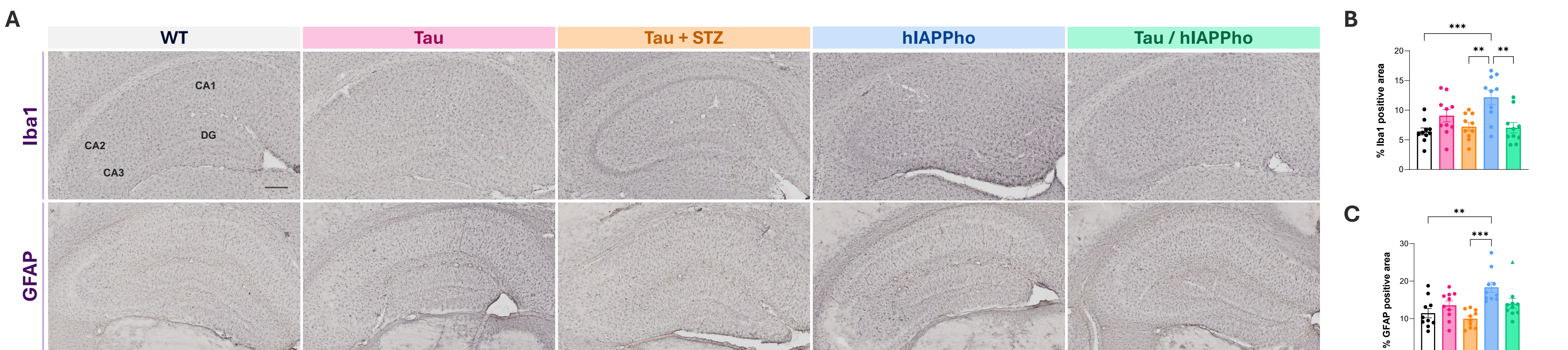


Figure 4. The overexpression of hIAPPPho drives hippocampal neuroinflammation, which is attenuated by tau co-expression. **A.** Representative hippocampal IHC micrographs for Iba1 and GFAP. DG: *Dentate Gyrus*; CA: *Cornu Ammonis*. Scale bar: 200 μ m. **B.** Quantification of % Iba1-positive area in the hippocampus. Statistics: One-way ANOVA ($F_{4,45} = 6.65$, p = 0.0003), followed by Holm-Šidák post-hoc. **C.** Quantification of % GFAP-positive area in the hippocampus. Statistics: Kruskal-Wallis test ($H_4 = 21.19$, p = 0.0003), followed by Dunn’s post-hoc. Data are presented as mean $\pm$ SEM. Significance: **p<0.01; ***p<0.001.

Conclusions

- ✓ Tau / hIAPPPho co-expression reduces lifespan with a prominent sex dimorphism.
- ✓ hIAPPPho impairs glucose homeostasis and exacerbates early hippocampal ptau pathology.
- ✓ hIAPPPho drives robust neuroinflammation, which is paradoxically attenuated by tau co-expression.