

Late-life depression as a driver of accelerated cognitive decline and amyloid- β pathology in an Alzheimer's disease model

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Introduction

According to recent research, depression may be a significant risk factor for Alzheimer's disease (AD) and cognitive impairment. AD and depression in later life are strongly correlated. Patients with mild cognitive impairment (MCI) and a history of depression have been shown to have an accelerated age of AD onset; women seem to be more susceptible to this condition. Furthermore, compared to MCI patients without depression, those with MCI who exhibit depressive symptoms have a higher burden of amyloid-beta ($A\beta$), the primary toxic protein linked to Alzheimer's pathology, and a higher risk of developing AD compared to non-depressed MCI patients. The induction of Alzheimer's pathology due to a depressive process has not been investigated under experimental conditions to mimic late-life depression as a risk factor for AD, despite the fact that some transgenic models of AD have been reported to develop signs similar to depression in advanced stages.

Methods

Subjects: APP751SL transgenic mice overexpress the human amyloid precursor protein (hAPP) harboring the familial Alzheimer's disease-associated Swedish (KM670/671NL) and London (V717I) mutations under the Thy1 promoter.

Depressive-like state tests: Splash test, forced swim test, adrenal gland weight, plasma corticosterone levels, and TPH enzyme expression.

Amyloid- β pathology: Thioflavin-S staining for fibrillar $A\beta$ deposits in hippocampus and ELISA quantification of soluble $A\beta$ 40 and $A\beta$ 42 in brain homogenate.

Analysis and quantification: Behavioral tests were analyzed using EthoVision XT17 (Noldus). Statistical analysis was performed with GraphPad Prism v9.

Conclusions

The results of our study indicate that the induction of CUMS in transgenic animals induces phenotypic changes related to a depressive state. Behavioral and histological studies suggest that depression-like induction can worsen AD pathology. The findings generated in this project could provide evidence of depression as a risk factor for AD, its mechanisms of action, use as early biomarkers, as well as the discovery of new therapies for AD. Research Foundation (27565 2018 NARSAD), the Intramural Funding Program of the University of Malaga (B1-2019_06), Operational Program FEDER Andalusia European Funds (UMA20-FEDERJA-104), and Ramon y Cajal Program (RYC-2017-21879), granted to IM-G.

Results

Analysis of CUMS-induction effect

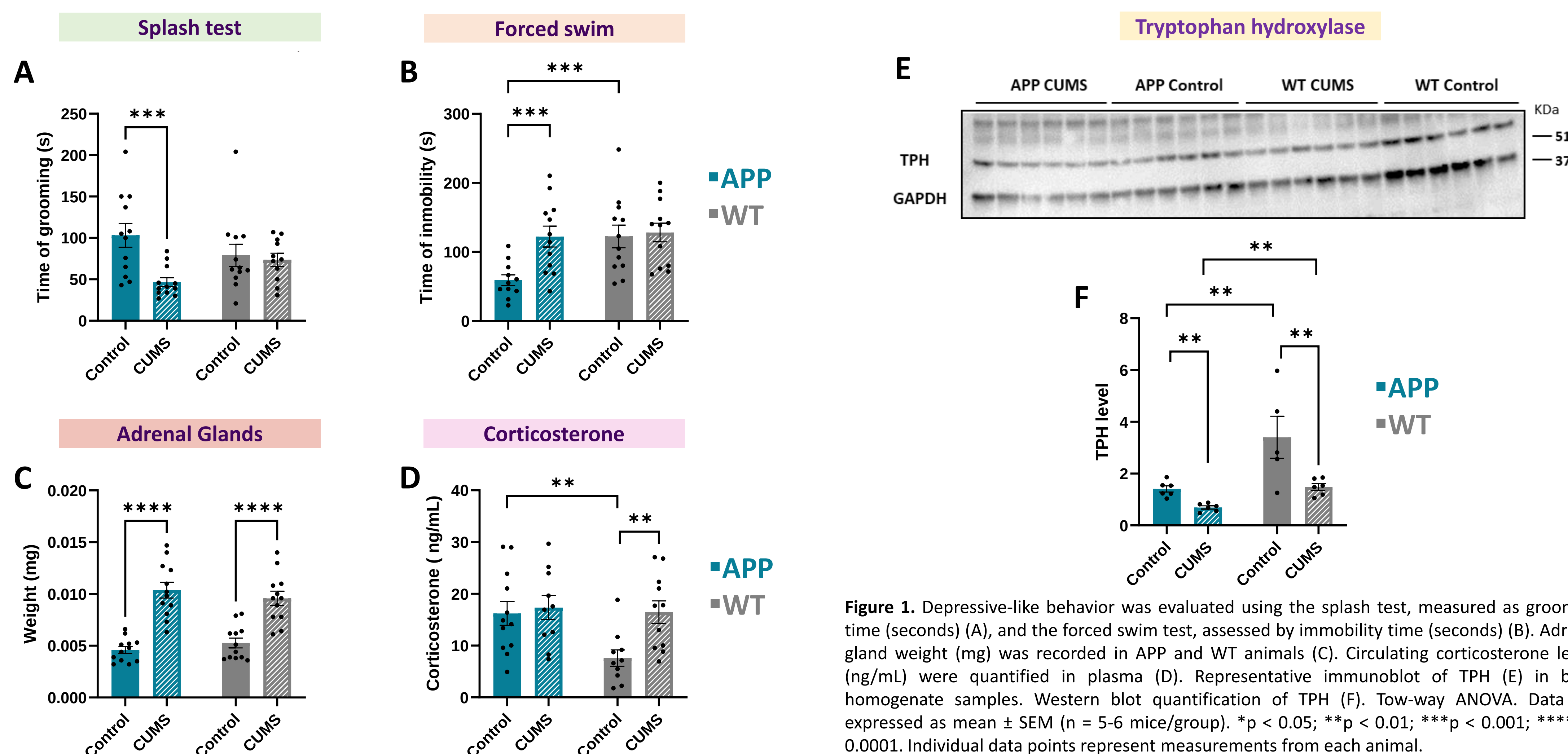


Figure 1. Depressive-like behavior was evaluated using the splash test, measured as grooming time (seconds) (A), and the forced swim test, assessed by immobility time (seconds) (B). Adrenal gland weight (mg) was recorded in APP and WT animals (C). Circulating corticosterone levels (ng/mL) were quantified in plasma (D). Representative immunoblot of TPH (E) in brain homogenate samples. Western blot quantification of TPH (F). Two-way ANOVA. Data are expressed as mean $\pm$ SEM (n = 5-6 mice/group). *p < 0.05; **p < 0.01; ***p < 0.001; ****p < 0.0001. Individual data points represent measurements from each animal.

Histological analysis of β -amyloid pathology after CUMS

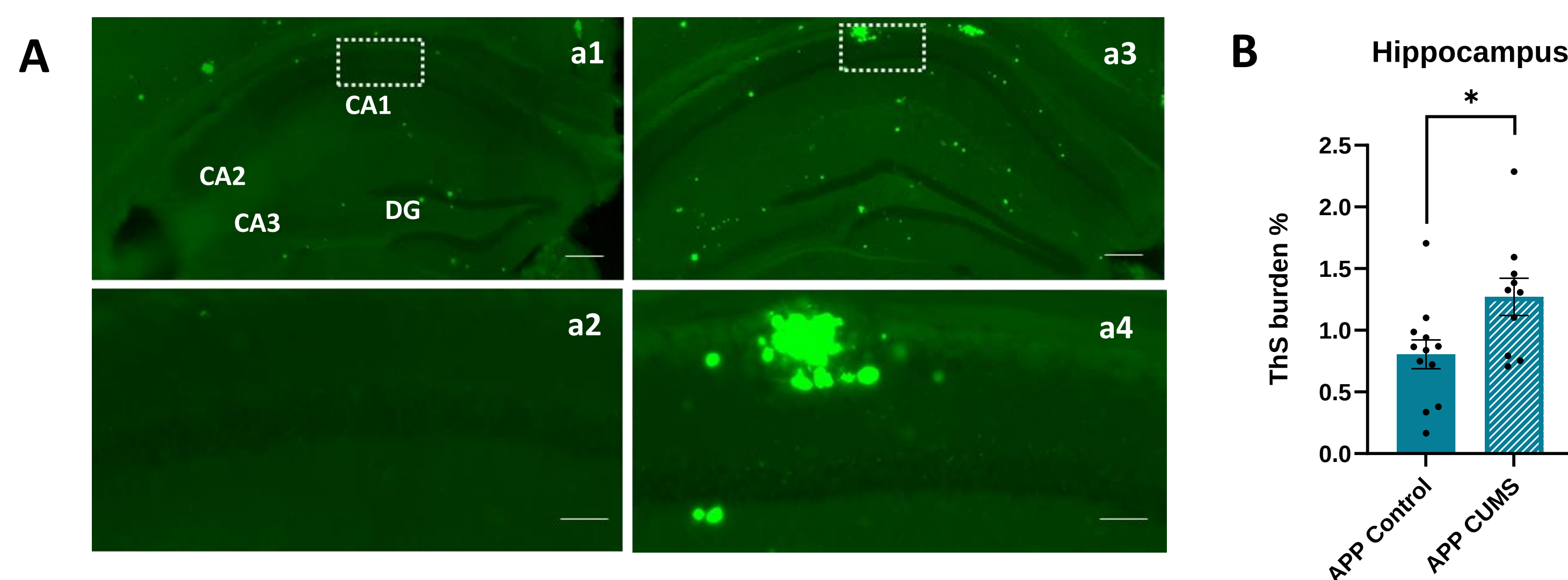
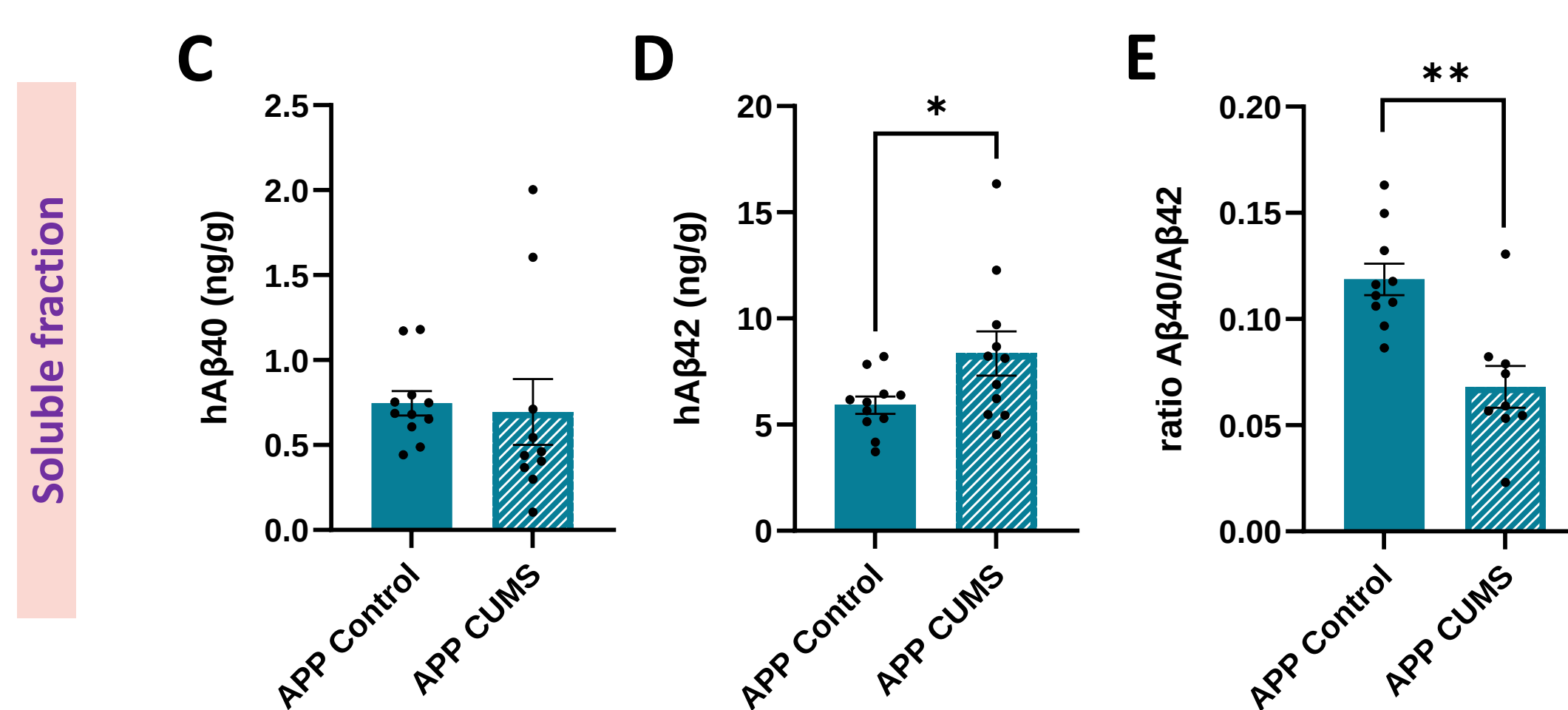


Figure 2. Representative images of Thioflavin-S (ThS) immunoreactivity in the hippocampus of APP animals (A); scale bars: 200 μ m (a1, a3), 50 μ m (a2, a4). Quantitative analysis of ThS burden (%) in the hippocampus (B). ELISA quantification of soluble $A\beta$ 40 (C), $A\beta$ 42 (D), and the $A\beta$ 40/ $A\beta$ 42 ratio (E), expressed as ng/g of brain tissue. Two-way ANOVA. Data are expressed as mean $\pm$ SEM (n = 5-6 mice/group). *p < 0.05; **p < 0.01. Individual data points represent measurements from each animal.



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