

Chronic cerebral hypoperfusion promotes the propagation of tau pathology through AEP-I₂^{PP2A} pathway

Xinyi Zhang¹, Shuai Zhao¹, Shahua Che¹, Siyan Zhong¹, Jia Shang¹, Yaping Yan¹, Ziqi Fan¹, Li Shang¹, Zhirong Liu¹, Baorong Zhang^{1*}, Yanxing Chen^{1*}
¹Department of Neurology, the Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, People's Republic of China.



Sunday-0281

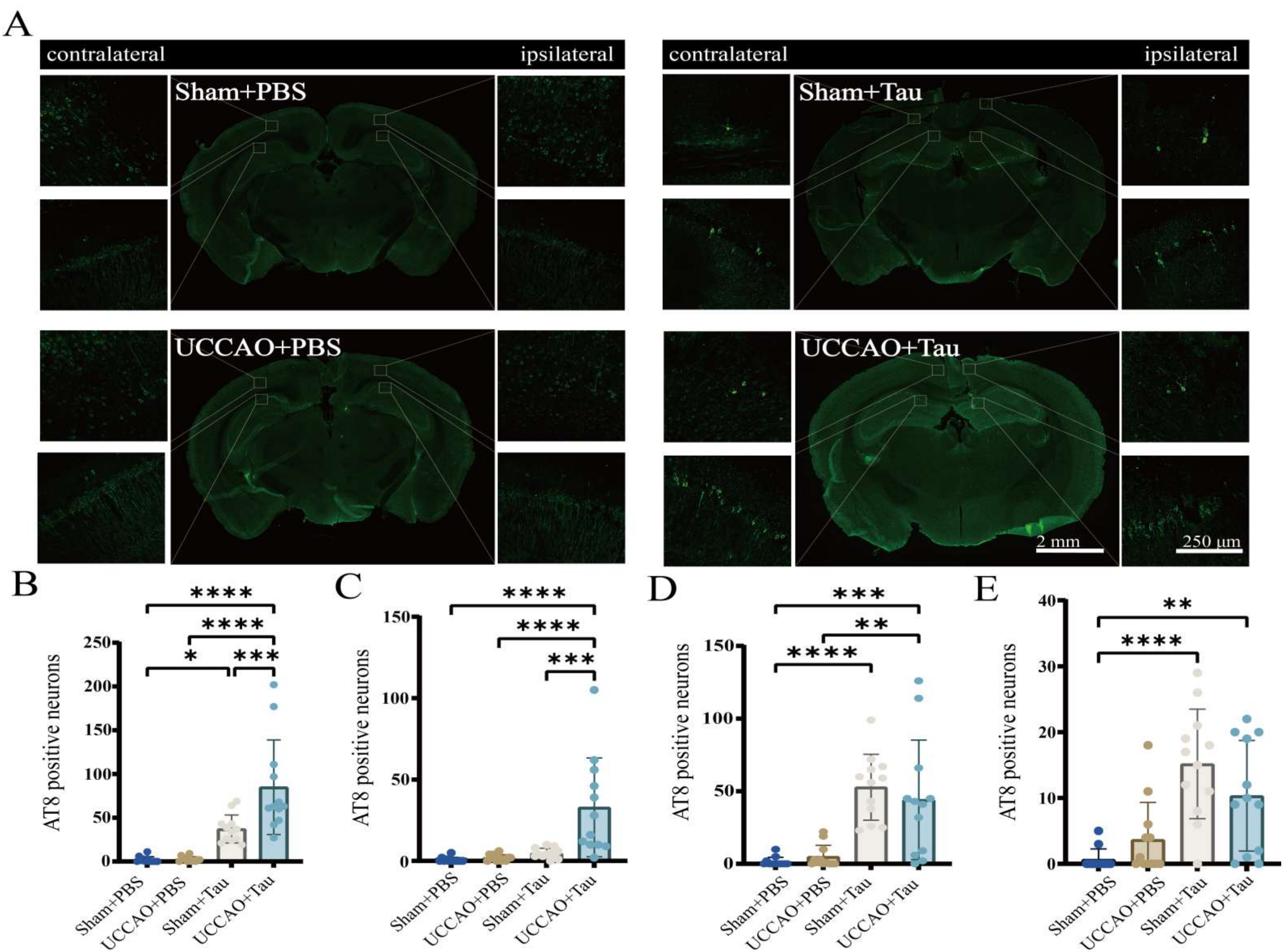
INTRODUCTION

The pathogenesis of Alzheimer's disease (AD), remains poorly understood. Neurofibrillary tangles (NFTs) are one of the main pathological changes. Chronic cerebral hypoperfusion (CCH) precedes tau pathology by years and may accelerate its progression. However, how CCH contributes to the propagation of tau pathology at the initial stage of tau aggregate formation and the underlying mechanisms remain elusive. Here, we aimed to investigate the effects of CCH on tau propagation.

METHODS

Tau PFFs were injected into the cortex and hippocampus of 2- to 3-month-old PS19 mice, followed by unilateral common carotid artery occlusion (UCCAO) to induce CCH. Western blotting and immunofluorescence staining were performed to analyze the propagation of tau pathology, the involvement of aspartate endopeptidase (AEP) and PP2A inhibitor (I₂^{PP2A}), and the activation of microglia in the brain. In addition, PS19 mice undergoing CCH and tau injection were orally administered the AEP inhibitor or vehicle to assess the therapeutic relevance of AEP blockade.

RESULT

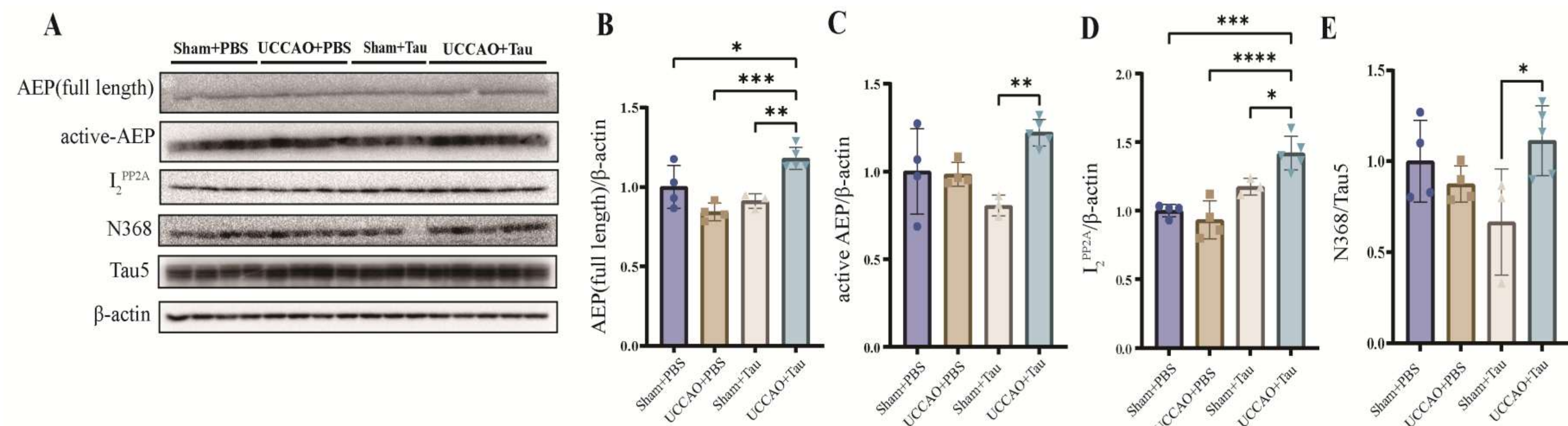


CCH accelerated the propagation of tau pathology in the brain

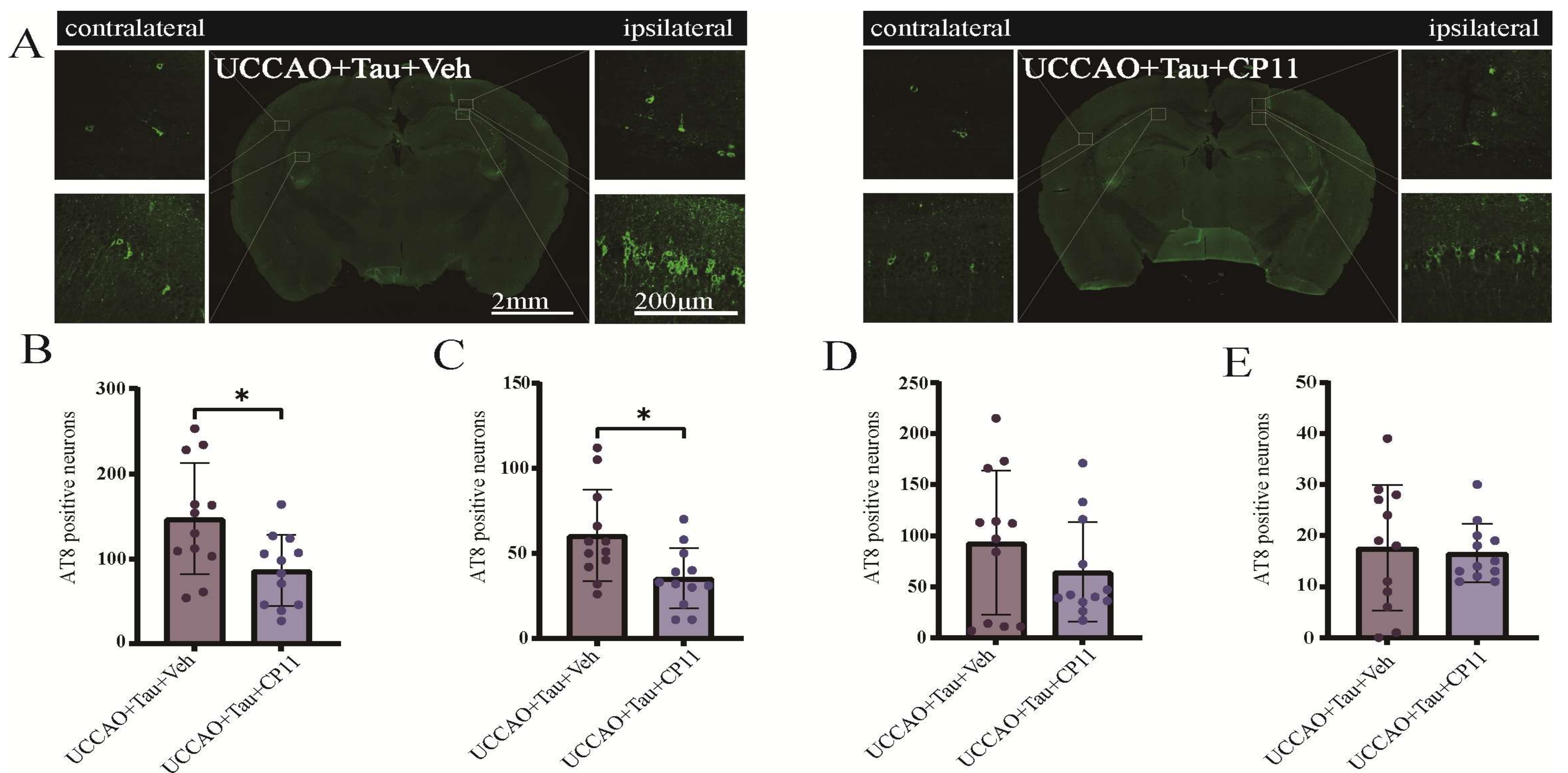
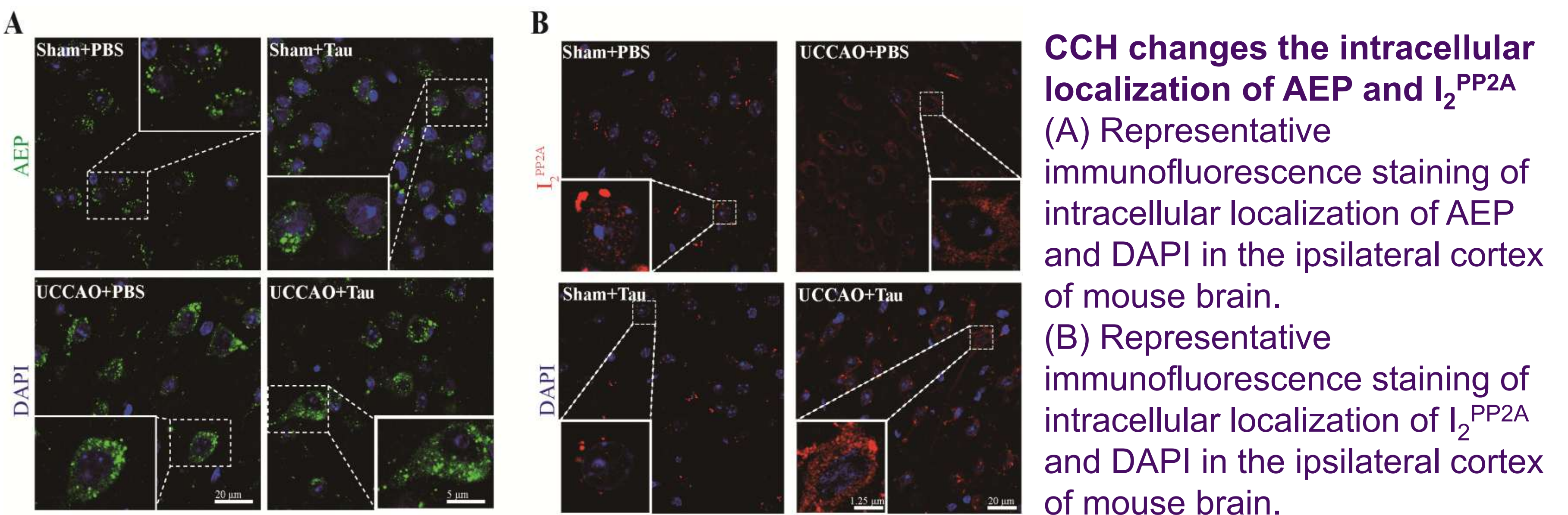
(A) Representative immunofluorescence images of aggregate-containing neurons in the whole mouse brain labeled with AT8 antibody. (B-E) Densitometric quantification of AT8 positive neurons in ipsilateral hippocampus (B), contralateral hippocampus (C), ipsilateral cortex (D), contralateral cortex (E) from different groups of mice.



RESULT



CCH upregulates the expressions of AEP- I₂^{PP2A} pathway proteins (A-E) Western blots of brain extracts from PS19 mice, developed with AEP, I₂^{PP2A} and N368 antibodies, and the relative immunoreactivity was calculated.



CP11 treatment alleviates hippocampal tau pathology

(A) Representative immunofluorescence images of aggregate-containing neurons in the whole mouse brain labeled with AT8 antibody. (B-E) Densitometric quantification of AT8 positive neurons in ipsilateral hippocampus (B), contralateral hippocampus (C), ipsilateral cortex (D), contralateral cortex (E) from different groups of mice

CONCLUSION

These data demonstrate that CCH accelerates the propagation of tau pathology, potentially involving activation of the AEP-I₂^{PP2A} pathway, suggesting AEP-I₂^{PP2A} signaling as a potential therapeutic target for early AD intervention.