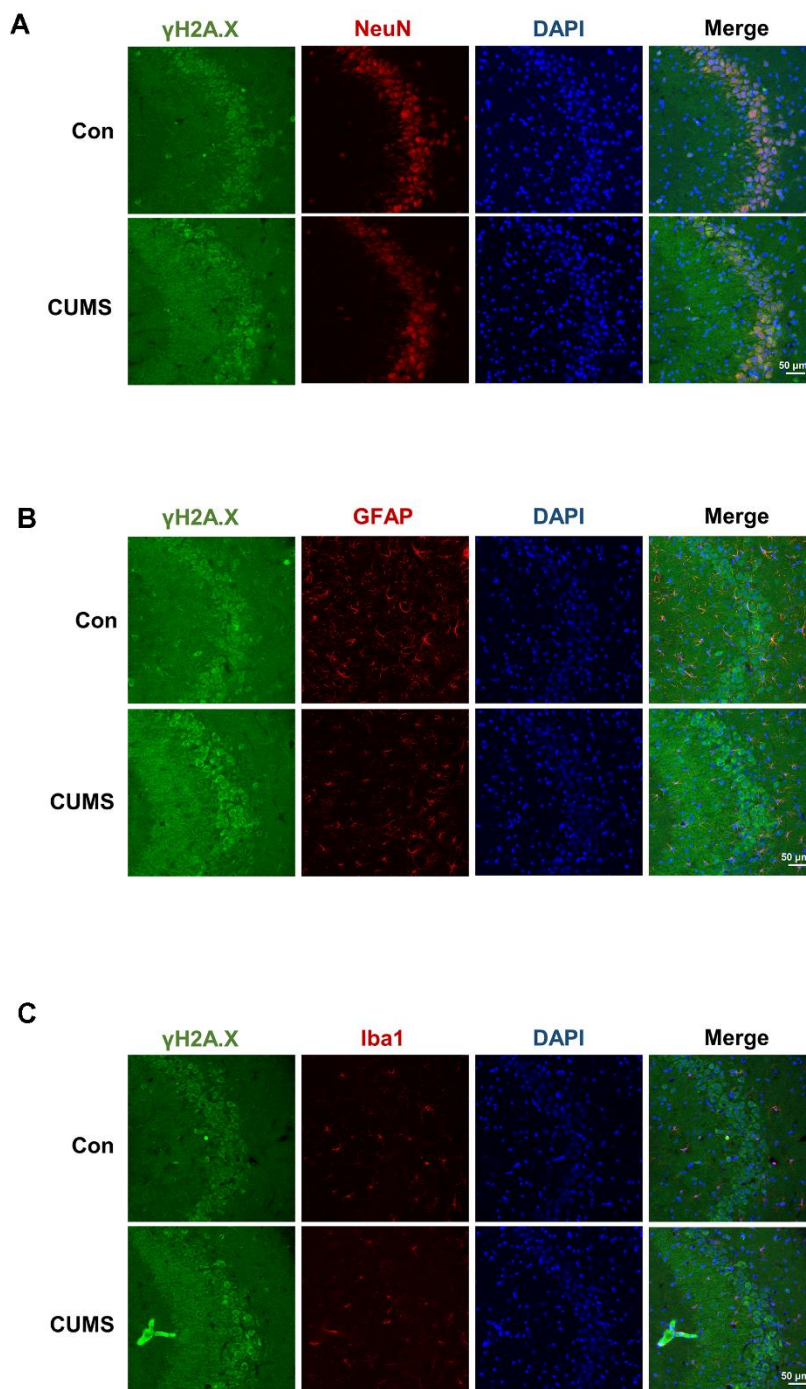
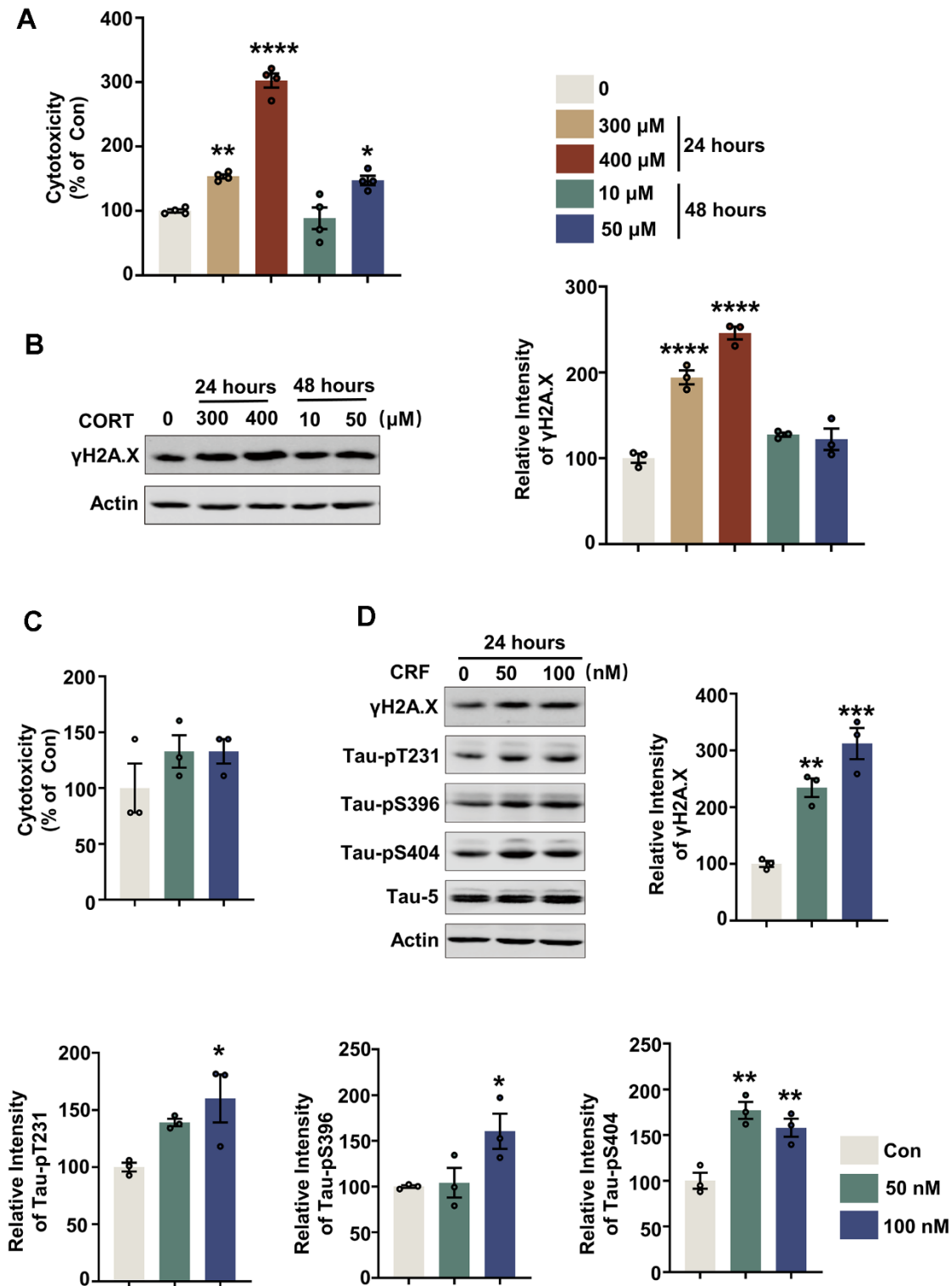


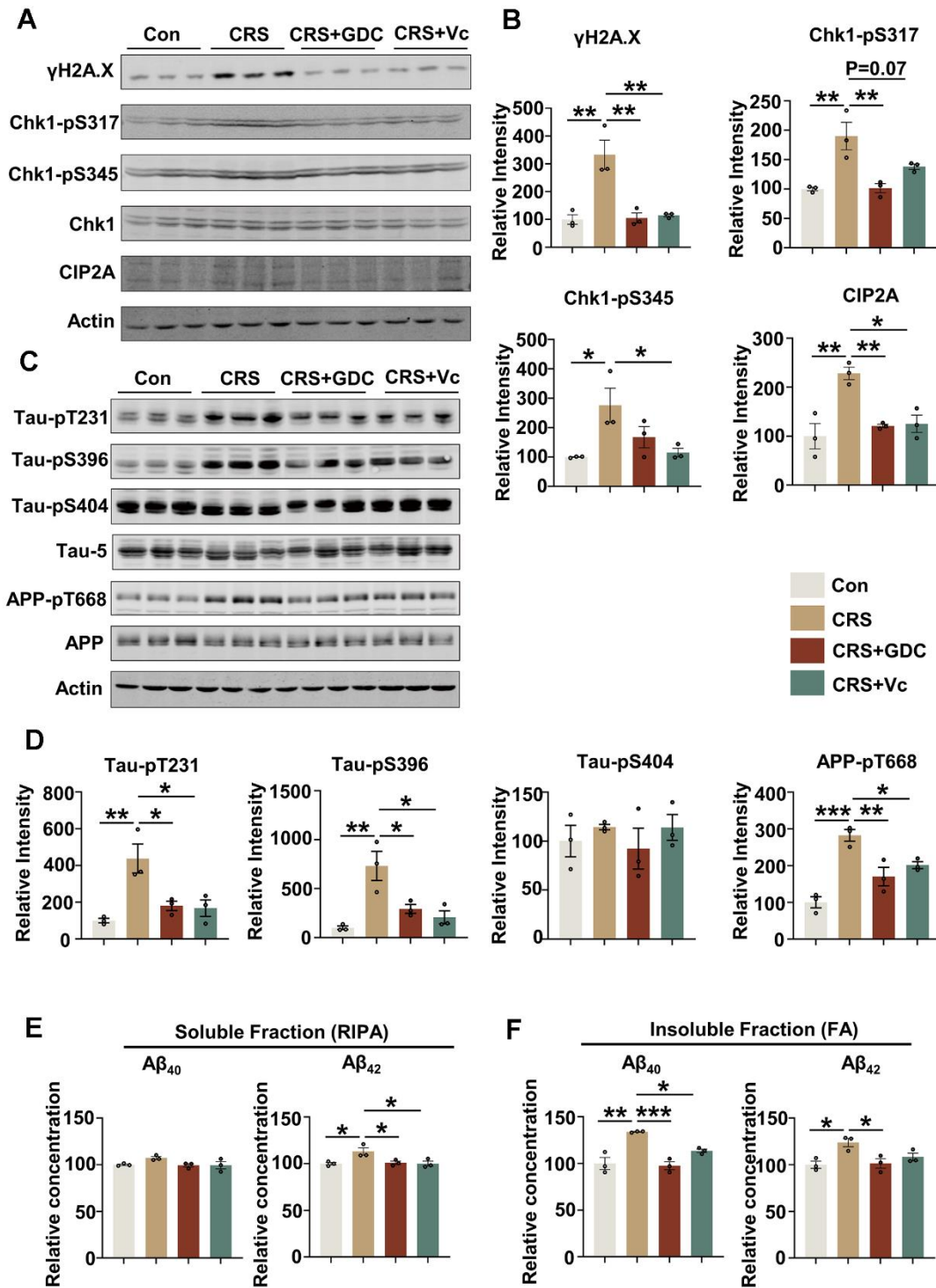
SUPPLEMENTARY FIGURES



Supplementary Figure 1. DNA damage mainly occurs in neurons, not in astrocytes or microglia. (A) Representative fluorescence images of γ H2A.X (green), NeuN (red) and DAPI (blue) in CA3 region of hippocampus in CUMS rats. Scale bar: 50 μ m. (B) Representative fluorescence images of γ H2A.X (green), GFAP (red) and DAPI (blue) in CA3 region of hippocampus in CUMS rats. Scale bar: 50 μ m. (C) Representative fluorescence images of γ H2A.X (green), Iba1 (red) and DAPI (blue) in CA3 region of hippocampus in CUMS rats. Scale bar: 50 μ m.



Supplementary Figure 2. CRF and CORT induce DNA damage in primary neurons. (A, B) Primary neurons were treated with 300 or 400 μM corticosterone (CORT) for 24 hours, 10 or 50 μM CORT for 48 hours. (A) LDH cytotoxicity assay results of the cells treated with CORT. n = 4 per group. (B) Representative immunoblots and quantification analysis of γH2A.X (normalized to the β-actin levels). n = 3 per group. (C, D) Primary neurons were treated with 50 or 100 nM CRF for 24 hours. (C) LDH cytotoxicity assay of the cells treated with CRF. n = 3 per group. (D) Representative immunoblots of γH2A.X, Tau-pT231, Tau-pS396, Tau-pS404, Tau-5 (total tau), and β-actin. And quantification analysis of γH2A.X (normalized to the β-actin levels), Tau-pT231, Tau-pS396, Tau-pS404 (normalized to the Tau-5 levels). n = 3 per group. All data represent mean ± SEM, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$.



Supplementary Figure 3. Vitamin C and Chk1 inhibitor reduce DNA damage, Chk1 activation and CIP2A expression, decrease tau phosphorylation and $A\beta$ levels in cortex of mice exposed to chronic stress. (A) Representative immunoblots of γ H2A.X, Chk1-pS317, Chk1-pS345, Chk1, CIP2A, β -actin in cortex of mice in different groups. (B) Quantification of the relative protein expression levels; non-phosphorylated proteins such as γ H2A.X and CIP2A were normalized to the β -actin levels; phosphorylated Chk1-pS317, Chk1-pS345 were normalized to total Chk1. $n = 3$ per group. (C) Representative immunoblots of Tau-pT231, Tau-pS396, Tau-pS404, Tau-5, APP-pT668, and APP, β -actin in cortex of mice in different groups. (D) Quantification of the relative protein expression levels; phosphorylated Tau-pT231, Tau-pS396, Tau-pS404 and APP-pT668 were normalized to Tau-5 and total APP respectively. $n = 3$ per group. (E) The $A\beta_{40}$ and $A\beta_{42}$ in soluble fraction of cortex tissues in different groups were detected by ELISA kit. $n = 3$ per group. (F) The $A\beta_{40}$ and $A\beta_{42}$ in insoluble fraction of cortex tissues in different groups were detected by ELISA kit. $n = 3$ per group. All data represent mean \pm SEM, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.