

Figure S1. DPA protects against KA-induced seizures in mice. Seizure evaluation was conducted after pretreatment with DPA for 2 h and KA injection. (A-C) Effects of DPA (0.5 mg/kg) on the seizure score, the number of seizure within 90 min and the seizure duration, respectively, in KA-treated mice. Seizure evaluation was carried out after KA injection. All the data were expressed as mean  $\pm$  SEM ( $n=6$ ). \* $p<0.05$ , \*\*\* $p<0.001$ . Abbreviation: DPA, D-penicillamine; KA, kainic acid.

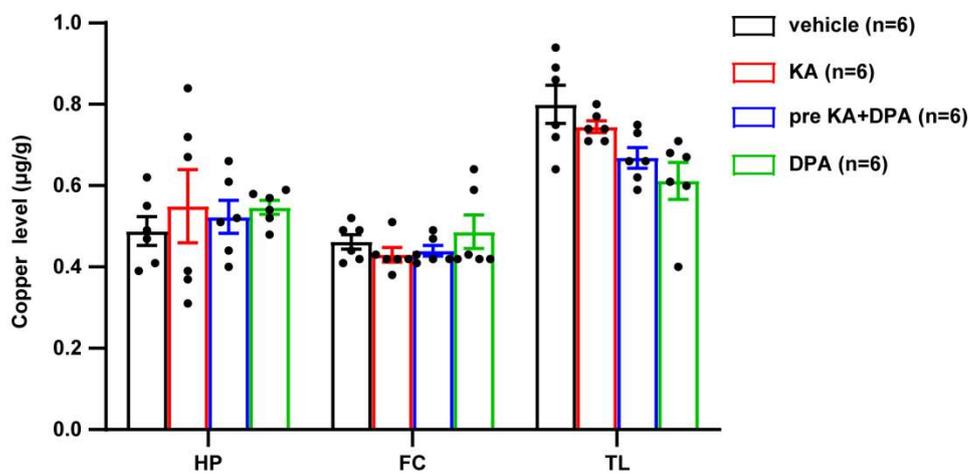


Figure S2. DPA does not alter the copper level in the brain tissues of KA-treated mice. Tissue samples from different brain regions including hippocampus, frontal cortex and thalamus were collected for detection of copper level following pretreatment with DPA (0.5 mg/kg) for 2 h and 3 d after KA (250 ng/ $\mu$ L) injection. All the data were expressed as mean  $\pm$  SEM ( $n=6$ ). Abbreviation: DPA, D-penicillamine; KA, kainic acid; HP, hippocampus; FC, frontal cortex; TL, thalamus.

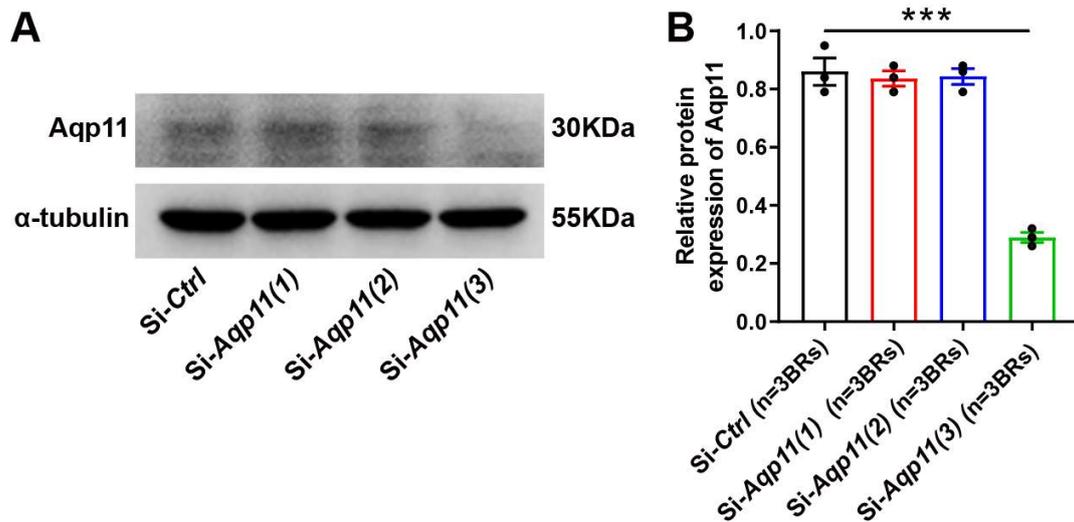


Figure S3. *Si-Aqp11 (3)* evidently decreases the protein expression of Aqp11 in HT22 cell. After transfection with three different si-RNAs of Aqp11 or matched control for 48 h, cell samples were collected for evaluating knock down efficiency by detecting Aqp11 protein expression. It was noted that transfection of *si-Aqp11 (3)* exhibited the most evident reduction of Aqp11 protein level. Thus, *si-Aqp11 (3)* was selected for the subsequent experiments. (A-B) show the representative blot images and statistical analysis. All the data were expressed as mean  $\pm$  SEM ( $n=3$  independent biological replicates). \*\*\* $p<0.001$ . Abbreviation: BRs, biological replicates.

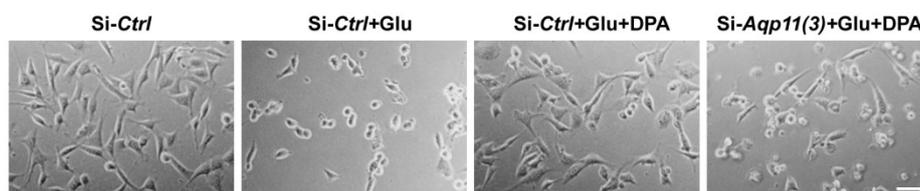


Figure S4. Knockdown of Aqp11 by siRNA transfection significantly blocks the protection of DPA against glutamate-induced cell death in HT22 cells. After transfection with three different si-RNAs of Aqp11 or matched control for 48 h, HT22 cells were cultivated in 24-well plate for 12 h. Then, DPA was pretreated for 2 h and subject to glutamate for another 8 h. Phase contrast images from each group were captured after glutamate challenge for 8 h. Scale bar indicates 50  $\mu$ m. Abbreviation: DPA, D-penicillamine; Glu, glutamate.

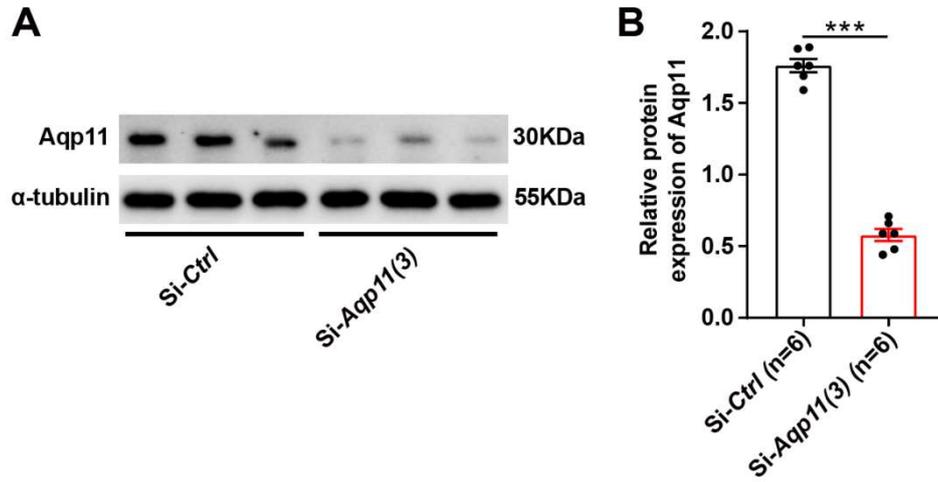


Figure S5. *Si-Aqp11 (3)* administration in vivo significantly results in the reduction of Aqp11 protein expression in mice hippocampus. Tissue samples were collected for western blot analysis after in vivo *si-Aqp11 (3)* administration for 48 h. (A-B) indicate the representative blot images and statistical analysis. All the data were expressed as mean  $\pm$  SEM ( $n=6$ ). \*\*\* $p<0.001$ .