Supplementary Figures legends

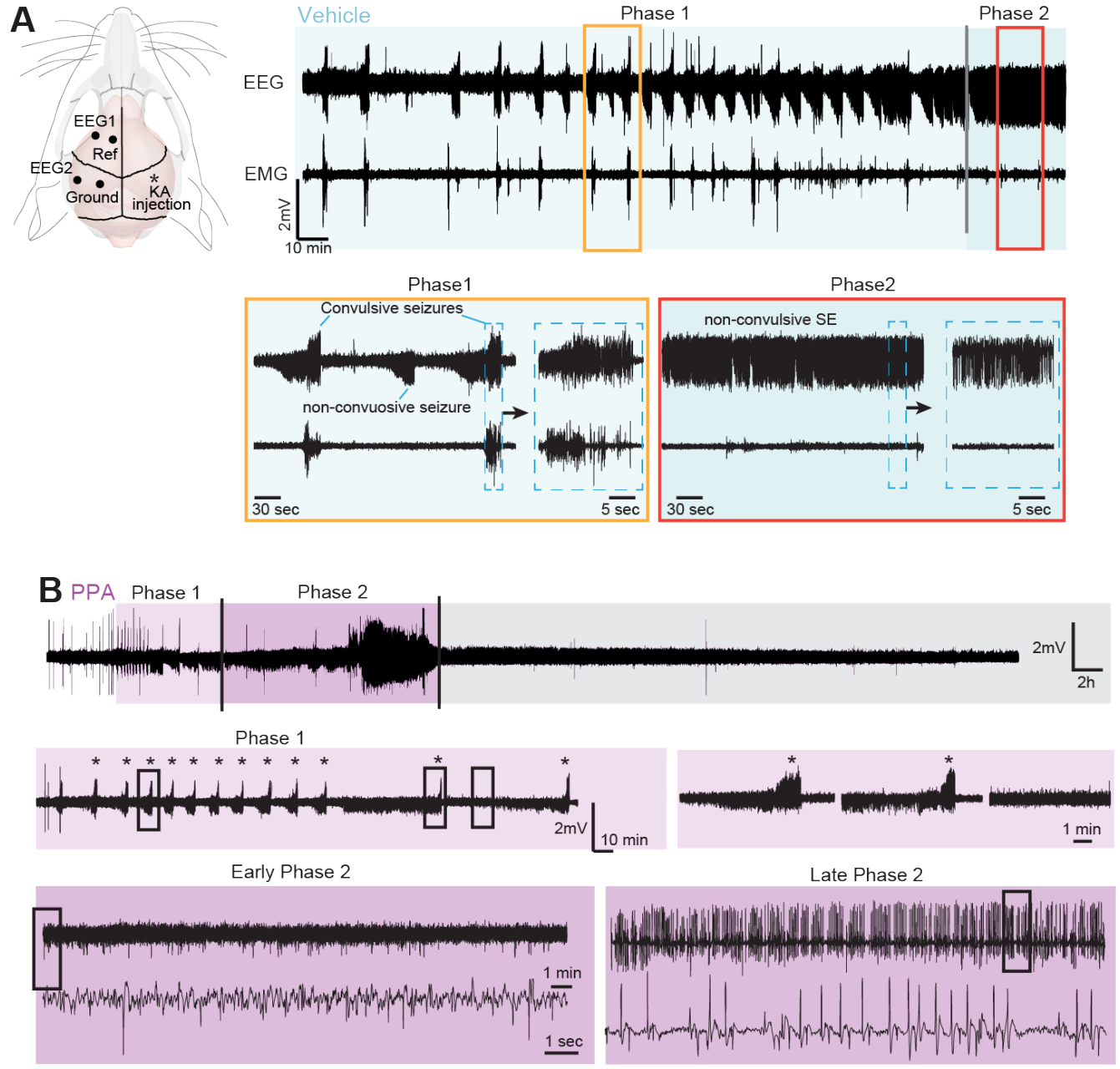

Fig. S1. Status epilepticus staging: Effect of pan-adrenergic inhibition. (A) The EEG electrode configuration (Left) and convulsive/non-convulsive seizures after intrahippocampal KA infusion in phase 1 and phase 2 (Right, scale bar, 2 mV, 10 min). Example EEG and EMG traces showed electrogenic seizures with or without muscle contraction. The regions marked by yellow or red box are magnified in the panels below. The repeated electrogenic seizures in phase 1 are either convulsive (tonic-clonic) or non-

convulsive (yellow box, scale bar, 30 sec), with atypical convulsive seizure (in the blue dash box), which is further magnified on the side (scale bar, 5 sec). After the transition to continuous spike-wave complex in phase 2, there was a substantial decline in muscular activity (red box, scale bar, 30 sec). A magnified view of repetitive epileptiform spiking activity is shown on the side (scale bar, 5 sec). **(B)** EEG characteristics of PPA-treated mice with intrahippocampal KA infusion. The EEG of PPA-treated mice showed similar patterns with vehicle-treated KA mice, namely the phase 1 with repeated convulsive seizures and phase 2 with non-convulsive status epilepticus as the sequel of phase 1. Examples of the repeated seizures in phase 1 and epileptic discharges in phase 2 are magnified in the lower panels. The asterisks indicate repeated seizures.

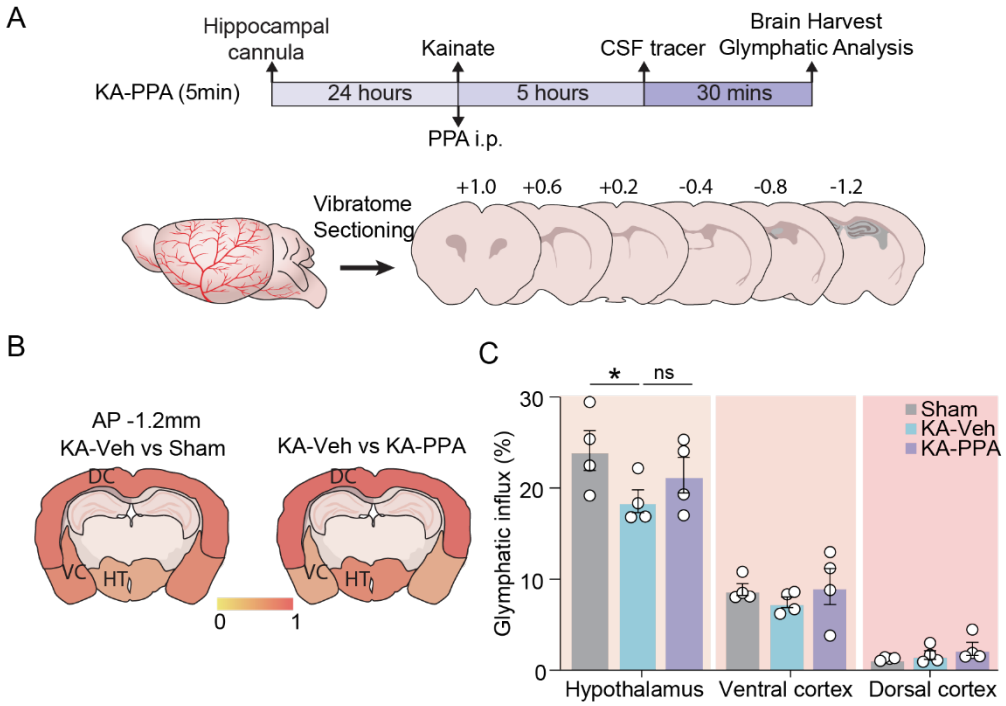

Fig. S2. Glymphatic influx after Acute KA infusion treated by PPA. **(A)** Glymphatic analysis of KA-induced status epilepticus and PPA treatment. A cisterna magna catheter (CM) was implanted 24 hours prior to the glymphatic evaluation. Five minutes after KA treatment, mice received vehicle or PPA and glymphatic function was evaluated five hours later by infusing CSF tracer (555-conjugated ovalbumin, OB-555, 45 kDa) in the CM. After 30 minutes of circulation, the brain was extracted and coronal brain sections (AP +1 ~ -1.2 mm) were cut using a Vibratome. **(B)** Regional analysis of CSF tracer distribution of coronal brain sections (AP -1.2 mm). The color-coded brain regions display the ratio of tracer distribution areas between KA-Veh and Sham-Veh groups (Left) and between KA-Veh vs KA-PPA groups (Right). **(C)** The comparisons among Sham-Veh, KA-Veh and KA-PPA are presented below, including brain regions of hypothalamus, ventral cortex, and dorsal cortex. (n = 4 each, Hypothalamus: Sham-Veh vs KA-Veh, $*P$ = 0.016; KA-Veh vs KA PPA, P =0.290, Two-way ANOVA, Tukey's multiple comparisons test). Data are presented as mean ± SEM.

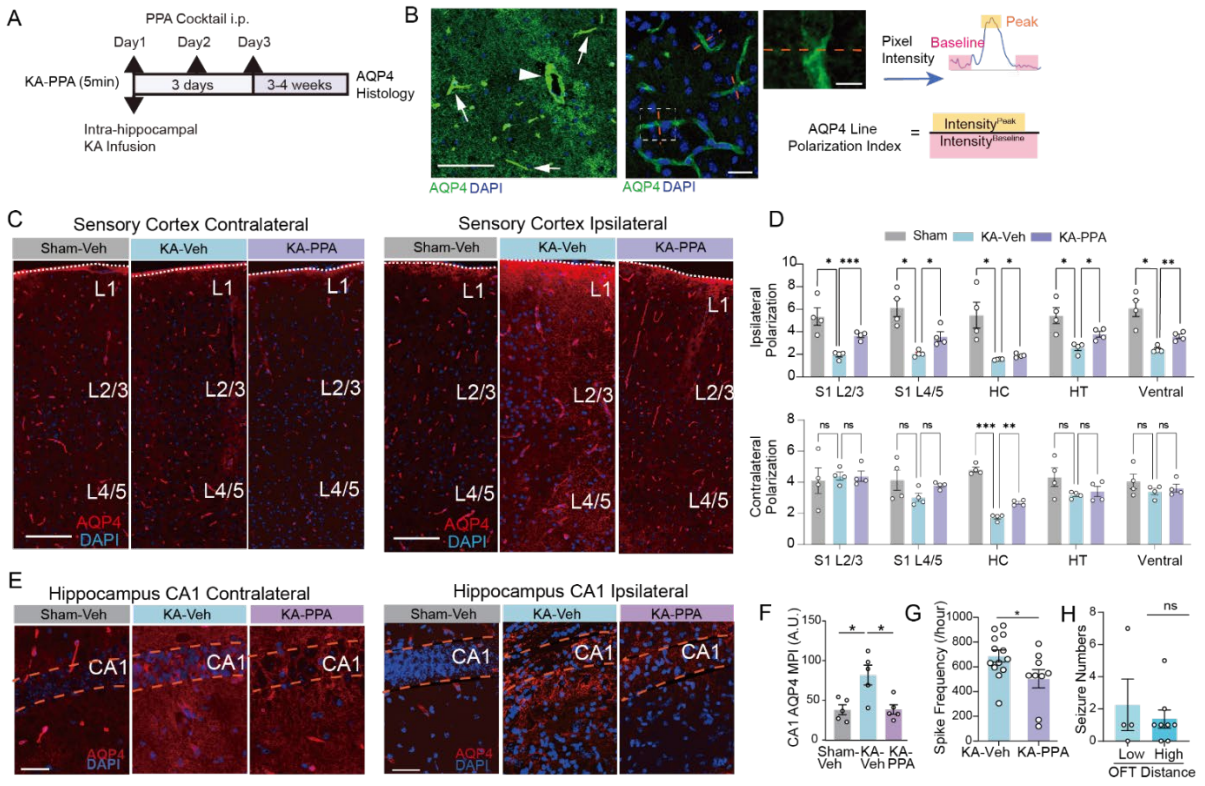

Fig. S3 Quantitation of AQP4 polarization in various brain regions. (A) Analysis of AQP4 immunostaining at 3-4 weeks after intrahippocampal KA infusion and PPA treatment. **(B)** Line-analysis of AQP4 polarization index (PI, see Methods for details). **(C)** Representative images of AQP4 expression in bilateral sensory cortex (scale-bar :100 μm). **(D)** Regional analysis of bilateral small vessel AQP4 PI Index in Sham-Veh, KA-Veh and KA-PPA, including sensory cortex layer 2/3, and layer 4/5, hippocampus, hypothalamus and ventral cortex. (*n* = 4 each, Two-way ANOVA, Tukey's multiple comparison. Upper Panel, Ipsilateral, Sensory cortex layer 2/3, Sham-Veh vs KA-Veh, **P* = 0.039; KA-Veh vs KA-PPA, ****P* <0.001; Sensory cortex layer 4/5, Sham-Veh vs KA-Veh, **P* = 0.026; KA-Veh vs KA-PPA, *P* =0.069; hippocampus, Sham-Veh vs KA-Veh, *P* = 0.082; KA-Veh vs KA-PPA, **P* =0.047; hypothalamus, Sham-Veh vs KA-Veh, **P* = 0.046; KA-Veh vs KA-PPA, **P* =0.031; ventral cortex, Sham-Veh vs KA-Veh, **P* = 0.029; KA-Veh vs KA PPA, ***P* =0.009. Lower Panel, Contralateral, Sham-Veh vs KA-Veh, ****P* < 0.001; KA-Veh vs KA-PPA, ***P* =0.001). **(E)** Representative images of AQP4 expression in bilateral hippocampal CA1 region (Scale bar, 50 μm). **(F)** Mean pixel intensity of AQP4 immunofluorescence in CA1 (n = 5 each, one-way ANOVA, Tukey's multiple comparisons test, Sham-Veh vs KA-Veh **P* = 0.011, KA-Veh vs KA-PPA **P* = 0.011). **(G)** The interictal spike frequency between KA-Veh and KA-PPA mice (KA-Veh (*n* = 13) vs KA-PPA (*n* = 9), **P* = 0.041, unpaired two-tailed t-test). **(H)** The seizure numbers in mice with less exploration (Total distance < 15 m) verse more exploration (Total distance > 15 m) in open field test (Low (*n* = 4) vs High (*n* = 8), *P* = 0.532). Data are presented as mean ± SEM.

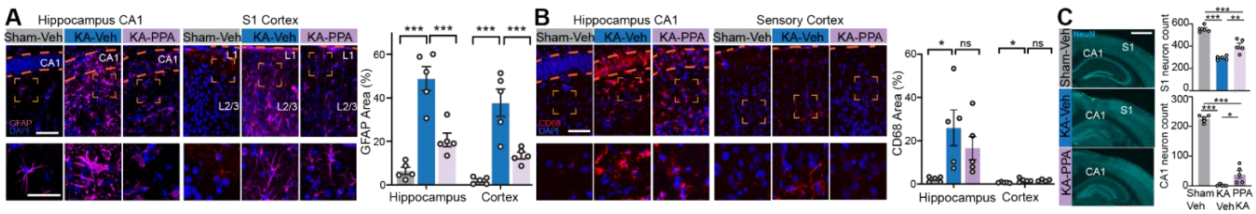

Fig. S4 Pan-adrenergic inhibition suppresses reactive gliosis in chronic epilepsy
(A) GFAP expression levels were analyzed in hippocampal CA1 and sensory cortex (S1). *n* = 5 each, ***P < 0.001, 1-way ANOVA, Sidak's multiple comparisons test. (Scale bar in upper image = 80 μm, lower image = 50 μm). **(B)** Confocal images of CD68 expression in hippocampal CA1 and sensory cortex (S1)**.** Hippocampus: Sham-Veh (*n* = 5) vs KA-Veh (*n* = 5), *P = 0.035; Cortex: Sham-Veh (*n* = 5) vs KA-Veh (*n* = 5), *P = 0.049, 1-way ANOVA, Sidak's multiple comparisons test. Scale bar in upper image = 80 μm, lower image = 50 μm**).** **(C)** Fluorescent images and neuron counting from NeuN immunostaining in CA1 and S1 regions (Scale bar = 1mm). *n* = 5 each. Hippocampus: Sham-Veh vs KA-Veh, ***P < 0.001, Sham-Veh vs KA-PPA, ***P < 0.001, KA-Veh vs KA-PPA, **P = 0.002; Cortex: Sham-Veh vs KA-Veh, ***P < 0.001, Sham-Veh vs KA-PPA, ***P < 0.001, KA-Veh vs KA-PPA, *P = 0.017, 1-way ANOVA, Tukey's multiple comparisons test. Data are presented as mean ± SEM.

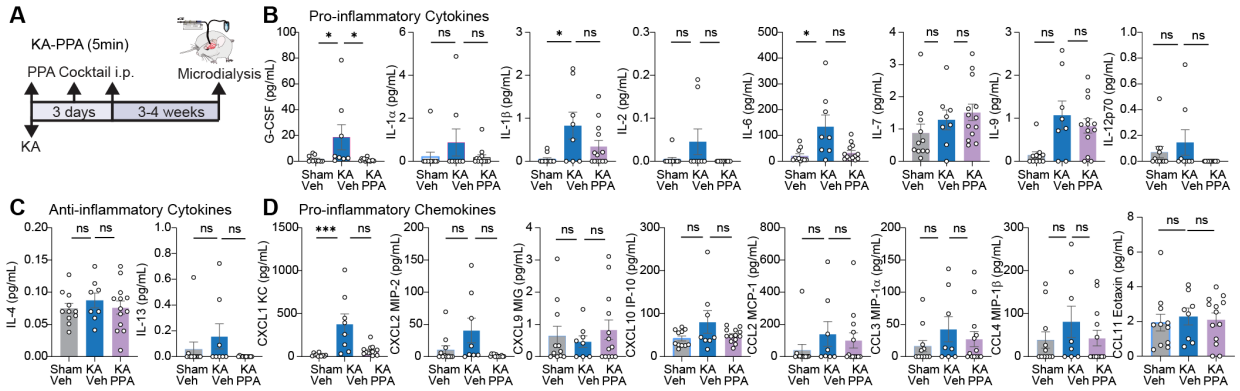

Fig. S5. Cytokines and chemokines in chronic epilepsy. (A) The timeline for cytokine sampling by intracerebral microdialysis followed by off-line analysis. The levels of **(B)** pro-inflammatory cytokines, **(C)** anti-inflammatory cytokines, and **(D)** pro-inflammatory chemokines. (Sham-Veh (n = 11) vs KA-Veh (n = 8) vs KA-PPA (n = 13). GSF: Sham-Veh vs KA-Veh, **P* = 0.020, KA-Veh vs KA-PPA, **P* = 0.026; IL-1β, Sham-Veh vs KA-Veh, **P* = 0.048; IL-6, Sham-Veh vs KA-Veh, **P* = 0.011; KC: Sham-Veh vs KA-Veh, ****P* < 0.001. IL-2, IL-4, IL-7, IL-12p70, IP 10, MIG, MIP-1a, MIP-1b, MIP-2 and Eotaxin use One-way ANOVA and Tukey's multiple comparisons test; G-CSF, IL-1a, IL-1b, IL-6, IL-9, IL-13, KC and MCP-1 use Kruskal-Wallis test and Dunn's multiple comparisons test). Data are presented as mean ± SEM.

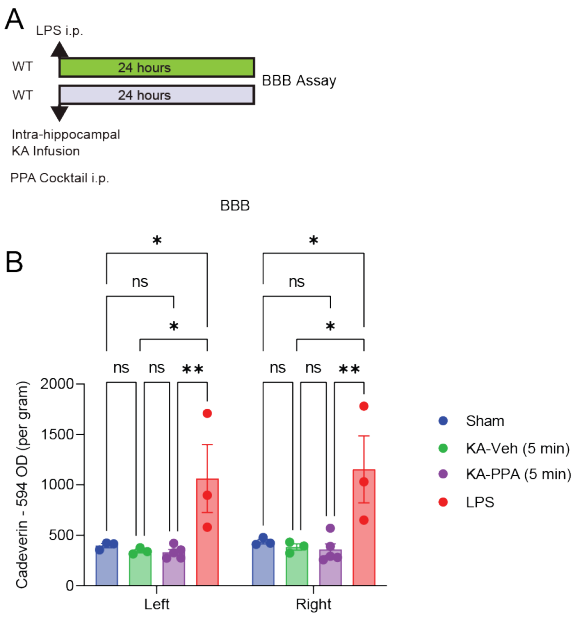

Fig. S6. The blood brain barrier (BBB) is not compromised at 24 hours after KA-induced SE. **(A)** To assay BBB permeability, we administered cadaverine-conjugate intravenously (refer to Method for details). As a positive control, we applied lipopolysaccharide (LPS; 10 mg/kg, i.p.) 24 hours prior to assaying the BBB permeability, and measured the brain penetration of intravenous cadaverine-conjugate ex vivo by recording the OD values (594 nm) in brain homogenates. Other groups of mice received vehicle, KA intrahippocampal infusion, or i.p. PPA 24 hours prior to the BBB test. For each hemisphere, OD values were normalized by tissue weight. **(B)** OD value comparison for each hemisphere. (Sham (n = 3) vs KA-Veh (n = 3) vs KA-PPA (n = 5) vs LPS (n = 3). Left, Sham vs LPS *P = 0.038, KA vs LPS *P = 0.022, KA PPA vs LPS **P = 0.008. Right, Sham vs LPS *P = 0.022, KA vs LPS *P = 0.013, KA PPA vs LPS **P = 0.004. Two-way ANOVA, Tukey's multiple comparisons test). Data are presented as mean ± SEM.

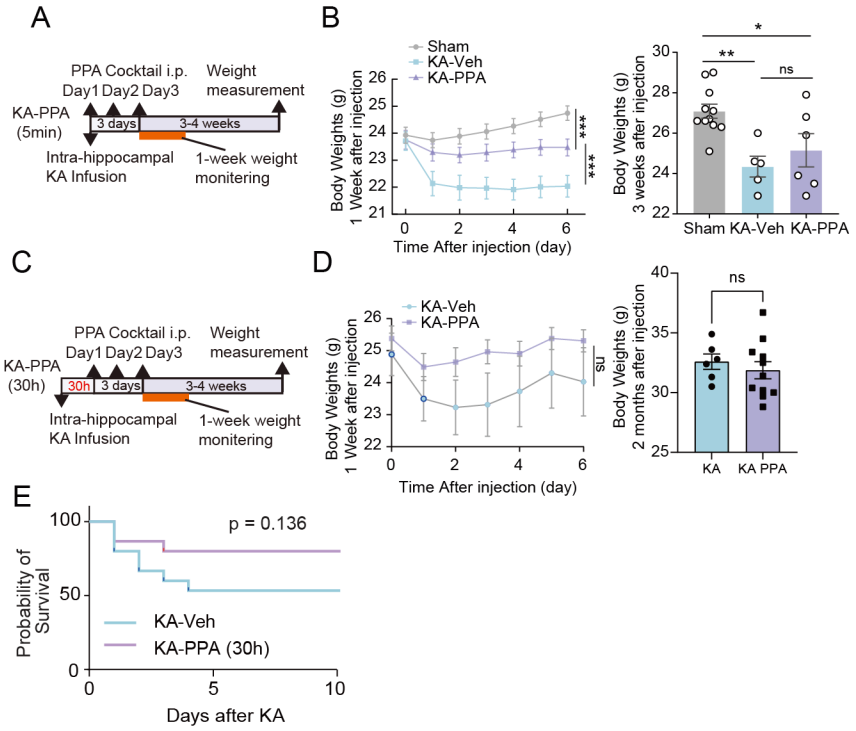

Fig. S7. Weight monitoring in post-KA mice.
(A) Body weight monitoring during epileptogenesis. Body weight was measured on days 1-7 and day 21 post-KA in KA-PPA (5 min) mice. **(B)** KA-PPA (5 min) prevented early weight loss at three weeks post-KA, but failed to rescue weight in the chronic stage (Left, early weight comparison, Sham-Veh (n = 12) vs KA-Veh (n = 11), ***P < 0.001, KA-Veh (n = 11) vs KA-PPA (n = 11), ***P < 0.001, two-way ANOVA, Tukey's multiple comparisons test. Right, weight in chronic stage, Sham-Veh (n = 10) vs KA-Veh (n = 5), *P = 0.008, KA-Veh (n = 10) vs KA-PPA (n = 6), *P = 0.046, one-way ANOVA, Tukey's multiple comparisons test). **(C)** Body weight was measured on days 1-7 and at day 21 post-KA in KA-PPA (30 h) mice. **(D)** Weight comparisons of KA-PPA (30h) and KA-Veh at early stage (KA-Veh (n = 7) vs KA-PPA (30h) (n = 11), days 1-7, treatment effect P = 0.178, Two-way ANOVA) and two months (right, KA-Veh (n = 6) vs KA-PPA (30h) (n = 11), two months, P = 0.525, unpaired two-tailed t-test). **(E)** Kaplan Meier survival curve after KA infusion (n = 15 each, KA-Veh vs KA-PPA (30 h), P = 0.136, Log-rank test). Data are presented as mean ± SEM.

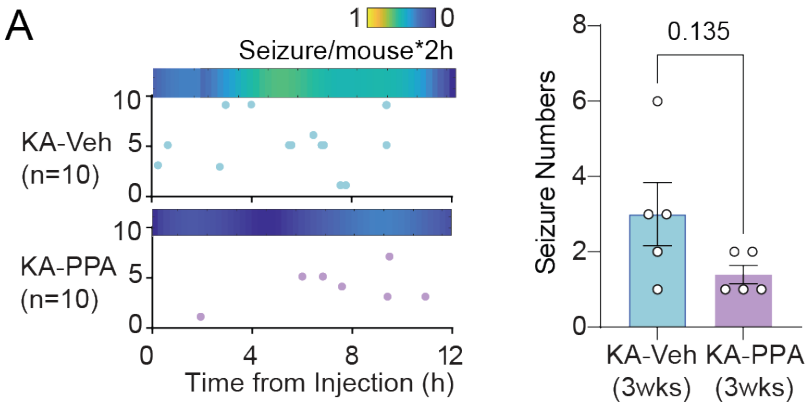

Fig.S8. Delayed PPA treatment in chronic epileptic mice does not reduce the number of seizures during the subsequent 12 hours.
(A) Representative plot of seizures to show onset distributions of PPA- or vehicle-treated epileptic mice during 12-hour recording sessions. Each horizontal line represents a mouse and each dot indicates a seizure. The heatmaps above indicates the seizure frequency of each group (left) and the number of spontaneous seizures (right). *n* = 5 each, seizure numbers, *P* = 0.135, two-tailed Mann-Whitney's test). Data are presented as mean ± SEM.