Inhibition of subicular seizure-tagged c-fos+ neurons alleviates cognitive deficit in epilepsy

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Abstract

Cognitive deficit is a common comorbidity in epilepsy and is not well controlled by current pharmacotherapy. Currently, how epileptic seizure affects cognitive performance remains largely unclear. The subiculum, the major output of the hippocampus, plays an important role in both coding cognitive function and seizure genesis. In this study, we sought to label the subicular seizure-activated c-fos+ neurons with a special promoter with enhanced synaptic activity-responsive element E-SARE in the subiculum, combined with chemogenetics, designer receptors exclusively activated by designer drugs (DREADDs), Ca^{2+} fiber photometry approaches, and behavioral tasks, to reveal the role of these neurons in cognitive impairment in epilepsy. Meanwhile, we also investigated the therapeutic potential of (+)-borneol in epilepsy models and its underlying mechanism. We found that chemogenetic inhibition of subicular seizure-tagged c-fos+ neurons (mainly CaMKIIα+ glutamatergic neurons) alleviates seizure generalization and improves cognitive performance in the hippocampal CA3 kindling epilepsy model. While inhibition of seizure-labeled c-fos+ GABAergic interneuron shows no effect on seizure and cognition. As a comparison, chemogenetic inhibition of the whole subicular CaMKIIα+ neuron impairs cognitive function in naïve mice in basal condition. Notably, histological and electrophysiological data indicated that inhibition of subicular seizure-tagged c-fos+ neurons enhances the recruitment of cognition-activated c-fos+ neurons via increasing neural excitability from synaptic integration. Importantly, we further found that (+)-borneol displays broad-spectrum anti-seizure potential in different experimental models via decreasing the subicular glutamatergic synaptic transmission without obvious side-effect. Our results demonstrate that subicular seizure-activated c-fos+ neurons contribute to cognitive impairment in TLE. This suggests seizure-tagged c-fos+ neurons as the potential therapeutic target to alleviate cognitive impairment in TLE and (+)-borneol as a promising anti-seizure compound

for pharmacotherapy in epilepsy

Keywords Epilepsy; cognitive deficit; (+)-borneol; subiculum; seizure-tagged c-fos+ neurons