Chemogenetic therapy strongly suppresses hippocampal excitability and spontaneous seizures in a rat model for temporal lobe epilepsy

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The hippocampus plays a crucial role in seizure generation in temporal lobe epilepsy (TLE), a common form of medication-resistant epilepsy. This preclinical study evaluated chemogenetics as a therapy for TLE. In this approach, excitatory neurons of the epileptic hippocampus were selectively inhibited through ligand-based activation of an inhibitory Designer Receptor Exclusively Activated by Designer Drugs (DREADD).

The intraperitoneal kainic acid rat model for TLE was used. Animals were injected in right hippocampus with adeno-associated viral vector carrying *CamKIIα-hM4Di-mCherry*. Two weeks after injection, rats were implanted with electrodes. Dentate gyrus excitability was assessed by recording perforant path evoked potentials (EPs; n=8) before and after activating DREADDs with subclinical doses of clozapine (0.1 mg/kg, s.c.). Seizure suppression was determined using continuous video-EEG recordings (n=7) during a baseline period of seven days and three days of treatment with clozapine (0.1 mg/kg/24h, s.c.).

Clozapine-induced activation of DREADDs suppressed synaptic transmission (field excitatory postsynaptic potential amplitude and slope reduced with 73%±12% and 65%±12% respectively) and postsynaptic neuronal activation (population spike surface area reduced with 53%±18) in dentate gyrus. In addition, in four of seven animals, DREADD activation led to complete suppression of spontaneous seizures for two to five hours.

Activating hM4Di DREADDs in excitatory hippocampal neurons decreases excitability of dentate gyrus and temporary suppresses spontaneous seizures in a rat model for TLE. We believe that after optimization, this technique will lead to prolonged seizure freedom, making it a promising tool for clinical applications.