Chemogenetic suppression of spontaneous seizures in a rat model for temporal lobe epilepsy

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Aim. The hippocampus is believed to play 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 potential therapy for TLE. Using 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).

Methods. The intraperitoneal kainic acid rat model for TLE was used. Animals (n=6) were injected in right hippocampus with adeno-associated viral vector carrying *CamKIIα-hM4Di-mCherry*. Two weeks after injection, rats were bilaterally implanted with depth electrodes in the dentate gyrus and CA1 region of both hippocampi. Seizure frequency before and after activating DREADDs with subclinical doses of clozapine was determined using continuous video-EEG recordings.

First, EEG was monitored during a baseline period of six days. Next, single injections of different clozapine doses (0.01, 0.1 or 1 mg/kg bodyweight/24h, s.c.) and vehicle were compared. For each dose, EEG was monitored during three days of treatment. Finally, one dose was selected to evaluate an improved dosing scheme in a randomized-blind trial. EEG was monitored during a baseline period of one days, followed by one day of treatment with clozapine (0.1mg/kg bodyweight/6h) or vehicle. In all experiments, seizure frequency during baseline recordings was used to normalize the data.

Results. Clozapine-induced activation of DREADDs had a dose-dependent seizure suppressing effect. Clozapine doses of 0.01, 0.1 and 1 mg/kg resulted in a clear lag in average cumulative seizure frequency of about 2, 5 and 8 hours respectively. Repeated clozapine administration resulted in a strong suppression of epileptic seizures in all animals tested. During treatment, the average daily seizure frequency was reduced with 86%±7% (SEM).

Conclusion. Clozapine-mediated activation of hM4Di DREADDs in excitatory hippocampal neurons temporary suppresses spontaneous seizures in a rat model for TLE in a dose-dependent way. Repeated clozapine administration results in a sustained suppression of epileptic seizures.