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Purpose: The hippocampus is believed to play a crucial role in seizure generation in temporal lobe epilepsy (TLE). Chemogenetic inhibition of excitatory neurons in the epileptic hippocampus using hM4Di, a Designer Receptor Exclusively Activated by Designer Drugs (DREADD), could be a novel way to reduce hippocampal excitability and suppress spontaneous seizures. We evaluated the effect of hM4Di, selectively expressed in excitatory hippocampal neurons, on excitability of dentate gyrus granule cells in non-epileptic rats and on seizure frequency in a rat model for TLE.

Method: Effect on granule cell excitability was assessed using perforant path evoked potentials (EPs) in seven non-epileptic rats. Animals were injected in right hippocampus with adeno-associated viral vector AAV2/7 carrying CamKIIα-hM4Di-mCherry (n=4) or sham construct (n=3) and implanted with electrodes. Five weeks after surgery, EPs were recorded before and after activating DREADDs using clozapine (0.1mg/kg, s.c.). Effect on seizure frequency was assessed in the intraperitoneal kainic acid (IPKA) rat model. Electrodes and cannulas were implanted bilaterally in intermediate hippocampi. Four weeks after surgery, DREADD (n=7) or sham construct (n=4) was injected through the cannula. Intracranial EEG was recorded for two weeks and rats were injected with clozapine (0.1mg/kg/24h, s.c.) during last five days of recording.

Results: Clozapine significantly decreased (-53%±13%) population spike amplitude for 17 hours post-injection, only in the hM4Di group. EP slope was not affected by clozapine. Despite the effect in non-epileptic animals, no significant change in average daily seizure frequency or duration was seen during clozapine treatment in IPKA rats.

Conclusion: Activating hM4Di DREADDs in excitatory hippocampal cells induces a prolonged decrease of intrinsic excitability of dentate granule cells in non-epileptic animals, but does not result in seizure-suppressing effects in the IPKA rat model for TLE. Whether the latter is due to insufficient suppression of neuronal excitability in the epileptic hippocampus, needs further investigation.