Chemogenetic suppression of excitatory hippocampal neurons in non-epileptic and epileptic rats

Goossens M-G[1], Christiaen E[2], Boon P[1], Vonck K[1], Van Den Haute C[3], Baekelandt V[3], Wadman W[1], Vanhove C[2], Raedt R[1]

[1] 4Brain Lab, Ghent University, Gent Belgium,
[2] Medisip, Ghent University, Gent, Belgium
[3] Department of Neurosciences, Katholieke Universiteit Leuven, Leuven, Belgium

The hippocampus plays 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 activating hM4Di, selectively expressed in excitatory hippocampal neurons, on excitability of dentate gyrus in non-epileptic and epileptic rats.

Dentate gyrus excitability was assessed using perforant path evoked potentials (EPs) in non-epileptic rats and in the intraperitoneal kainic acid (IPKA) rat model. Animals were injected in right hippocampus with 2x3µL AAV viral vector carrying CamKIIα-hM4Di ($n_{CTR\text{-}DREADD}$=3, $n_{IPKA\text{-}DREADD}$=8) or sham construct ($n_{CTR\text{-}SHAM}$=2). Two weeks after injection, rats were implanted with electrodes and EPs were recorded before and after activating DREADDs using clozapine (0.1 mg/kg, s.c.).

In animals expressing hM4Di DREADDs, clozapine administration resulted in a shift in I/O curve towards higher intensities. Surface of the (largest) population spike was reduced in both control (-97%±2%) and epileptic (-53%±18%) rats at stimulation intensities corresponding to saturation of the EP and population spike in the untreated condition. In addition, total field potential amplitude and slope were lower in both groups after clozapine (-91%±3% and -81%±2% respectively in control rats; -73%±12% and -65%±12% respectively in epileptic rats). In rats that received the sham vector, no such effects could be observed.

Activating hM4Di DREADDs in excitatory hippocampal cells induces a decrease of excitability of dentate granule cells in both non-epileptic animals and in the IPKA model for TLE.