The effect of chemogenetic hippocampal suppression on evoked potentials and seizures in a multifocal rat model for temporal lobe epilepsy

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Rationale. To date, about one third of epilepsy patients cannot be helped using conventional medication. Therefore, there is a need for alternative therapies. Selective neuronal inhibition using Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) have been proven a useful tool in preclinical epilepsy research. In this study, it was evaluated whether long-term DREADD-mediated seizure suppression could be obtained in the intraperitoneal kainic acid (IPKA) rat model for temporal lobe epilepsy, when DREADDs were selectively expressed in excitatory hippocampal neurons.

Methods. IPKA rats received unilateral hippocampal injections of adeno-associated viral vector containing genes for the inhibitory DREADD hM4Di, preceded by a cell-specific promotor targeting excitatory neurons. Naïve IPKA rats were included as control group. The effect of clozapine-mediated DREADD activation on dentate gyrus evoked potentials (DGEPs) was evaluated (n_{CTR} = 3; n_{DREADD} = 10). Next, the effect of DREADD activation on spontaneous seizures was examined using continuous electroencephalography. Animals were systemically treated with single (0.1 mg/kg/24h) and repeated (0.1 mg/kg/6h) injections of clozapine (n_{CTR} = 5; n_{DREADD}=6). Finally, long-term continuous release of clozapine (n_{DREADD}=10) and olanzapine (n_{DREADD}=7) using implantable osmotic minipumps (both 2.8 mg/kg/7d) was evaluated. All treatments were administered between 1.5 and 13.5 months after vector injection. Immunohistology was performed to visualize DREADD expression.

Results. Inhibition of DGEPs was observed after clozapine treatment in the DREADD group. Only in DREADD-expressing animals, a single dose of clozapine reduced seizure frequency during the first six hours post injection. When clozapine was administered every six hours, seizures were suppressed during the entire day. Both clozapine and olanzapine resulted in a significant seizure-suppressing effect during the first four days of the continuous treatment, after which tolerance developed. Histological analysis revealed DREADD expression in both injected and non-injected hippocampi, as well as some extrahippocampal expression in cortical regions. Unfortunately, lesions at the site of injection were also observed.

Conclusions. This study shows that inhibition of the hippocampus using chemogenetics results in potent seizure suppressing effects in the IPKA rat model, even months after vector injection. It indicates that – despite the obvious need for optimization – chemogenetic neuromodulation could contribute to a more optimal treatment for temporal lobe epilepsy.

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