Targeting aberrant KAinate Receptors in Temporal Lobe Epilepsy (KARTLE)

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In humans, the predominant form of epilepsy - a chronic brain disease whose hallmarks are disturbed activity of nerve cells and recurrent seizures - is called temporal lobe epilepsy or TLE. Unfortunately, forty percent of all TLE patients do not respond well to the current generation of pharmaceutical drugs, thus creating an urgent need for novel therapeutic and clinically relevant approaches. Here, we aim to fill in this critical gap, by expanding on our data that a certain type of cell surface molecules (aberrant synaptic kainate receptors, KARs) markedly contribute to epileptiform activity in TLE patients within a specific region of the brain (dentate gyrus [DG], located in the hippocampus area). The central goal of our project is therefore to design and validate two parallel strategies to target aberrant synaptic KARs, in order to inhibit their activity and thereby alleviate the disease symptoms in TLE patients. In the first strategy, we will devise and characterize new pharmacological agents that selectively target and block aberrant synaptic KARs, and will then study their anti-epileptic activity in mouse models of TLE. In the second strategy, we will exploit a cellular mechanism of gene silencing called RNA interference (RNAi) to achieve the same goal, i.e., to remove aberrant syanptic KARs. To efficiently and specifically deliver the molecules inducing anti-KAR RNAi to DG cells, we will engineer gene transfer vehicles based on non-pathogenic Adeno-associated viruses (AAV). Identical to the first strategy, these new AAV/RNAi vectors will then also be tested for anti-KAR activity in mouse models of TLE. Finally, we will additionally validate the best candidates from both strategies in hippocampal tissues that were surgically extracted from TLE patients. As a whole, our project will extend pre-clinical studies in cells and animals to pathophysiologically most relevant human epileptic tissue, which should pave the way for future clinical translation of our innovative approaches.