O-46

Neuropeptide-Based Gene Therapy for Treatment of Focal Epilepsy

Alexandra S. Agostinho[1], Mario Mietzsch[2], Luca Zangrandi[1], Iwona Kmiec[1], Anna Mutti[1], Larissa Kraus[3,5], Pawel Fidzinski[3], Ulf C. Schneider[4], Martin Holtkamp[3,5], Christoph Schwarzer[1], and **Regine Heilbronn**[2,5]

[1]Department. of Pharmacology, Medical University of Innsbruck, Austria; [2]Institute of Virology, Campus Benjamin Franklin, Charité - Universitätsmedizin Berlin, Germany; [3]Department. of Neurology, Charité - Universitätsmedizin Berlin, Epilepsy Center Berlin-Brandenburg, Germany; [4]Department of Neurosurgery, Charité - Universitätsmedizin Berlin, Germany [5]Berlin Institute of Health (BIH), Berlin, Germany

Focal epilepsy represents one of the most common chronic CNS diseases. The high incidence of drug resistance and insufficient responsiveness to surgery pose unmet medical challenges. Patients are at high risk to develop devastating comorbidities. In the quest of novel, disease-modifying treatment strategies neuropeptides represent promising candidates. Our solution is based on AAV gene therapy to transduce neuropeptide precursors into the epileptogenic focus in well-accepted mouse and rat models of chronic, drug-resistant temporal lobe epilepsy. The aim is to restore the exhausted neuronal supply of seizure-dampening peptides, allowing their locally restricted release “on demand”. We provide the proof of concept that AAV-mediated dynorphin expression in an established epileptogenic focus leads to complete suppression of seizures over months. Supporting data from peptide action on human hippocampal slice electrophysiology suggest a high translational potential. In mice the debilitating long-term decline of spatial learning and memory is prevented. Moreover, lost learning and memory capabilities are regained in chronic epilepsy. Neuronal dynorphin expression is focally restricted and its release dependent on high-frequency stimulation, as it occurs at the onset of seizures. The novel format of “drug on demand” delivery is viewed as a key to prevent habituation and to minimize the risk of adverse effects, leading to long-term suppression of seizures and of their devastating sequelae.