GluCl as an epileptic seizure autoregulatory Gene therapeutic approach

Reporting

Project Information

AutoStopS

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Periodic Reporting for period 1 - AutoStopS (GluCl as an epileptic seizure autoregulatory Gene therapeutic approach)

Reporting period: 2016-07-15 to 2018-01-14

Summary of the context and overall objectives of the project

Around 70 Million people worldwide are affected by epilepsy (estimates for Europe 0.6-0.7% of the general population) (http://www.who.int/mediacentre/factsheets/fs999/en/; accessed 10/05/2015), of whom at least 20% (14 million people) do not respond to commonly available drugs. Many antiepileptic drugs show a relatively narrow therapeutic window, and elicit a variety of serious side effects, mainly because they affect the whole brain. The only effective treatment option for focal-onset refractory epilepsy is surgical resection, where the region in which the epileptic seizures arise is removed. Although this invasive surgery can result in seizure freedom in 60 – 80% of patients, it is accompanied by a substantial risk of severe and irreversible side effects, including disturbance in motor function, vision, memory and language. This risk makes surgery inappropriate for the overwhelming majority of patients. New treatment options are therefore urgently required. Several mechanisms that make neuronal networks hyper-excitable have been identified in experimental and clinical epilepsy. Increased activity of excitable synapses, and subsequent increased synchronized glutamate (glu) release, is a common feature of these pathologies, and closely related to the definition of seizures as episodes of abnormal and excessive discharge of principal neurons. We developed a biochemical sensor which detects high levels of the excitatory neurotransmitter glu, which is increased in the cerebrospinal fluid (of patients) during seizures. In response to the increased glu concentration the sensor opens, and triggers an inhibitory Chloride current in affected neurons. This approach has the potential to decrease the disease-burden of a high number of epilepsy patients, for which currently no appropriate treatment options are available.

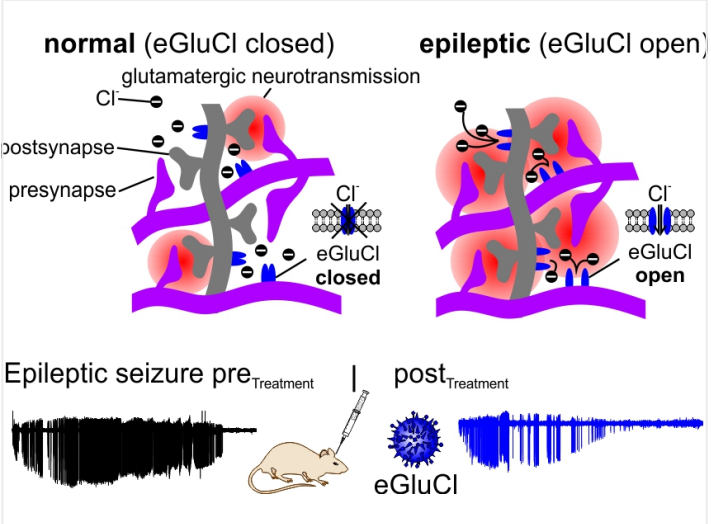
Work performed from the beginning of the project to the end of the period covered by the report and main results achieved so far

During AutoStops we were able to develop a novel gene therapeutic approach which is able to autoregulate neuronal excitability and thereby inhibit epileptic seizure generation and generalization. For this purpose, a DNA plasmid encoding the glutamate-gated chloride channel (GluCl) from C. elegans is transferred into affected brain regions, exploiting a virus as shuttle. In the course of this project, the DNA plasmid had to be adapted to detect the levels of the excitatory neurotransmitter glu common during epileptic seizures (eGluCl). Furthermore, eGluCl was tested in two independent models of acute and chronic epilepsy. In addition we were able to show that eGluCl opens an inhibitory Chloride conductance just on demand, minimizing its potential side-effect profile. The results of AutoStopS have been presented at national and international scientific conferences, and will be published in a peer-reviewed scientific journal.

Progress beyond the state of the art and expected potential impact (including the socio-economic impact and the wider societal implications of the project so far)

In epilepsy research, encouraging results have been obtained with gene therapies in different animal models. Early attempts used strategies to achieve a permanent reduction in neuronal or circuit excitability, for instance using potassium channel overexpression. Although this may be better tolerated than irreversible surgical resection it carries the theoretical risk of side effects in the treated

brain region. Newer approaches are limited in their translational applicability, as they require biocompatible activators with a fast mode of action and/or implantable devices. In contrast, with AutoStopS we aimed to establish a treatment strategy which detects and stops seizures generation in a biochemical autoregulatory mode of action. Therefore, prevention of seizure generation does neither need implantable devices nor patient intervention. Furthermore, as AutoStops gets only activated on demand, no adverse effects have been observed.
Recent years have seen enormous advances in viral vectors as delivering shuttles to overexpress transgenes of interest in vivo. In the last 6 month 3 novel gene-therapies were approved by the Federal Drug Agency. This highlights the importance of this area of research in the development of novel drug strategies, tackling the socioeconomic burden of severe diseases. With AutoStopS we were able to be part of this development and propose a novel autoregulatory strategy to detect seizure generation and generalization.



eGluCl opens an inhibitory Chloride conductance on demand.

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