AMERICAN EPILEPSY SOCIETY

EPILEPSY CURRENTS

The Journal of the American Epilepsy Society

VOLUME 13 ■ SUPPLEMENT 1

AES 2012 Abstract Supplement - Epilepsy Currents Online

AES 2012 Annual Meeting

November 30 – December 4, 2012, San Diego, CA, USA

Abstracts

Results: From Cadence software simulations, the ASICs operate at 1.8V and on average, consume under 700 uW during non-stimulating conditions. The constant current stimulator drives ~170 uA across a 10 kOhm load, and the neural amplifier has 58 dB gain with approximately 1.5 kHz bandwidth. Empirical results from the ASICs are presented.
Conclusions: Previously, our group has demonstrated LED based optical coupling, far field RF powering, and an ultralow power seizure detection ASIC. Integration of all these technologies into a singular device results in a first generation RF powered, closed-loop electrical or optical stimulator.

3.062
XENOTRANSPLANTATION OF PORCINE FETAL NEURONAL STEM CELLS (PNSCS) IN EPILEPSY - A FEASIBILITY STUDY IN AN ACUTE SEIZURE RAT MODEL
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Rationale: Xenotransplantation from genetically modified ("humanized") pigs provides a possible solution to the shortage of human organs for allotransplantation. Porcine fetal neuronal stem cells (PNSCs) are promising for treatment of neurological diseases, including pharmacoresistent epilepsy to overcome the shortage of human fetal neuronal stem cells and the ethical restrictions associated herewith. Clinical trials employing PNSCs grafted in patients suffering from different neurological disorders revealed repair of synaptic connections and restoration of behavioral deficits albeit the cells died shortly after transplantation. Further clinical studies were stopped because of potential risks of zoonotic infections emanating from porcine endogenous retroviruses (PERVs) that are integrated into the pig genome. However, recently the interest in porcine xenografts resumed after PERV-free pigs became available and cells or organs from transgenic pigs for xenotransplantation increasingly became available. Here, we compare wild-type versus transgenic PNSCs in their anticonvulsant efficacy in an acute seizure model, their survival rate after grafting, and integration into the host tissue.
Methods: Wild-type and transgenic PNSCs were isolated from the medial ganglionic eminence and were cultivated as neurospheres. They were transplanted bilaterally into the substantia nigra pars reticulata (SNr) of adult rats. The SNr is a key structure in seizure propagation and modulation in several experimentally induced seizure types. The putative anticonvulsant efficacy was evaluated by the intravenous pentylenetetrazol seizure threshold test before and at different time-points after grafting (from 10 days up to 3 months). Survival rate, differentiation, and integration of grafted cells were histologically analyzed after termination of the experiments.
Results: Initial results revealed that wild-type PNSCs survived, at least in part, until the end of the experiment. However, grafting of the cells into the SNr failed to induce anticonvulsant effects at any investigated time point. Wild-type PNSCs differentiated into neurons and astrocytes and showed expression of the GABA-synthesizing enzyme glutamic acid decarboxylase after grafting. In future studies we will be using different types of transgenic porcine cells (hA20, hHO-1), and hope to increase the amount of surviving GABA-producing cells to induce anticonvulsant effects.
Conclusions: These preliminary results show the feasibility of grafting PNSCs into the SNr in an acute seizure rat model. Future studies will include cells from humanized PERV-free PNSCs to minimize the risk of cross-species infections and rejection.

3.063
POSSIBLE EFFECT OF LOW CURRENT TRANSCRANIAL FOCAL STIMULATION VIA TRIPOLAR CONCENTRIC RING ELECTRODES ON BEHAVIORAL SEIZURE ACTIVITY INDUCED BY PENTYLENETETRAZOLE IN RATS
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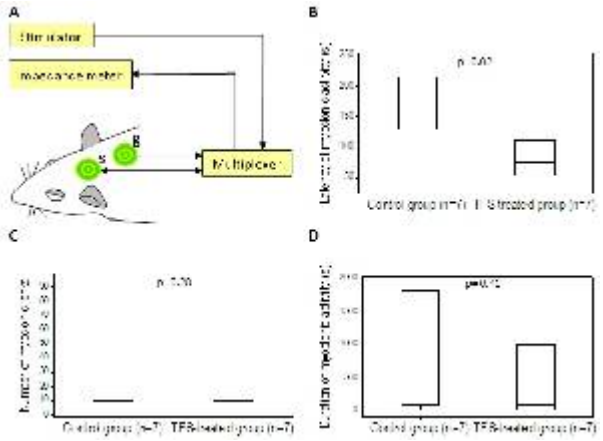
Rationale: Recently we demonstrated the effectiveness of noninvasive transcranial focal electrical stimulation (TFS) via tripolar concentric ring electrodes (TCRE) to control pentylenetetrazole (PTZ) induced seizures in rats. In [1] we showed TFS lessens behavioral seizure activity of recurrent PTZ administrations. In [2] a noninvasive seizure control system based on automatic seizure detection triggering the TFS reduced electrographic seizure activity power in the treated group. In our previous work the TFS current intensity was 50 mA, now we report on the potential effect of 5 mA TFS on PTZ-induced seizure activity which is comparable to the current intensity of transcranial direct current stimulation (tDCS) that can be applied to humans.
Methods: Naive male Sprague-Dawley rats were used in this study. The TCREs were placed on the scalp with conductive paste and adhered with dental cement 24 h before the experimental procedure (Fig. 1A). The animals were divided into control (n = 7) and TFS-treated (n = 7) groups based solely on skin-to-electrode impedance. If impedances between the three recording surfaces of TCRE (s) and the isolated ground TCRE (g) were less than 10 KΩ the rat was administered TFS. PTZ (45 mg/kg ip) was given to both groups and TFS (5 mA, 200 μs, 300 Hz, 2 min, biphasic, charge-balanced pulses) was triggered manually in the TFS-treated group only when the first myoclonic jerk (MJ) was observed. To score behavioral seizure activity we adapted the revised Racine's scale from [1] (Table 1). The latency of initial myoclonic activity was defined as the time to the first MJ. The maximal score value and the total number of MJs were counted (first to last) for each animal as well as the duration of myoclonic activity (time elapsed between the first and the last MJs). The non-parametric Mann-Whitney U test was used to make comparisons between the control and TFS-treated groups due to non-normality.
Results: The latency of myoclonic activity was significantly different ($p = 0.02$; Fig. 1B) with medians of 169 s and 74 s for the control and the TFS-treated group, respectively. At the same time there was no significant difference in maximal behavioral seizure activity score ($p = 0.41$; both medians equal to 3), number of myoclonic jerks ($p = 0.28$; medians of 12 and 10; Fig. 1C), and duration of myoclonic activity ($p = 0.41$; medians of 165 s and 100 s; Fig. 1D).
Conclusions: The latency of myoclonic activity could not have been affected by TFS in either group since TFS was not turned on until the first MJ was observed. Statistically longer latency in the control group stems from lower initial susceptibility of this group to PTZ. Combined with an absence of any statistically significant differences in the other three metrics affected by TFS this suggests an anticonvulsant effect of TFS at low currents.

Stages of the revised Racine's scale for PTZ-induced seizures in rats used to score seizure-related behavioral activity

Category	Behavioral expression
0	No seizure activity
1	Sudden behavioral arrest and/or motionless staring
2	Myoclonic jerk (sudden and fast neck jerk)
3	Clonic seizure in a sitting position
4	Clonic seizures while lying on the belly
5	Tonic-clonic seizure while lying on the belly
6	Tonic-clonic seizures while lying on the side and/or wild jumping



Translational Research: Biomarkers

3.064
MAGNETIC RESONANCE IMAGING WITHIN HOURS OF EXPERIMENTAL FEBRILE STATUS EPILEPTICUS PREDICTS SUBSEQUENT EPILEPSY

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Rationale: A subset of children with febrile status epilepticus (FSE) develop temporal lobe epilepsy, however, it is not possible to predict who will be affected. If a prognostic biomarker can be identified, it will facilitate the development of preventative therapies and enable targeted intervention. In both children and rats, magnetic resonance imaging (MRI) has identified acute hippocampal abnormalities after FSE. However, it is not known if the increased T2 in children is a marker of epileptogenesis, and late (1 month after FSE) changes in rats were not predictive. We used an animal model of FSE in which ~45% of rats develop temporal lobe epilepsy, and a high-field 11.7T MRI scanner to search for a clinically relevant early marker of epileptogenesis.
Methods: FSE-experiencing rats (n=19), normothermic (n=14) and hyperthermic controls (n=14) underwent MR imaging using an 11.7T Bruker MRI system. Rats were imaged at 2, 18, and 48 hours following FSE. Multi-slice multi-echo T2-weighted images were acquired, T2 relaxation time maps were generated, and T2 values were measured in several regions of interest (ROI), including the hippocampus and the amygdala. The development of spontaneous seizures was monitored over the following eight months using continuous video EEG recordings. ROC curves was used to assess potential biomarkers. Youden's index (sensitivity+specificity-1) was used to indicate maximum potential effectiveness of a biomarker.
In a separate group of rats, the physiological basis of the T2 changes was investigated. To test the possibility that they were generated by a paramagnetic effect of deoxyhaemoglobin (dHb, FSE (n=13) and normothermic controls (n=8) were imaged at the 2-hour time point, followed by blood analysis to quantify the dHb levels (by Radiometry; OSM-3 co-oximeter).
Results: T2 signal abnormalities were present in MRI scans obtained at 2hours after FSE in a subset of the FSE rats. Specifically, T2 decreases were found, unlike previous studies performed at later time points and with lower magnetic fields. At high magnetic fields, paramagnetic substances such as dHb are known to reduce T2. Therefore, we examined the relationship between T2 decreases and dHb levels following FSE, and found a significant correlation between T2 and dHb levels (Pearson correlation=-0.54, p=0.014). Thus, T2 decreases may indicate increased oxygen consumption (and hence more deoxygenated hemoglobin) following FSE. Five of nineteen FSE rats developed spontaneous seizures. Reduced T2 in the amygdala (AUC=0.83±0.21 95%CI, p=0.033) was predictive of epilepsy with an optimal threshold yielding 80% sensitivity and 14.3% false positive rate. At this threshold there is a positive predictive value of 66.7% and a negative predictive value of 92.3%.
Conclusions: Decreased MRI T2 relaxation time in the amygdala 2h following FSE differentiate rats that eventually become epileptic from those that do not. Furthermore, these decreases suggest that increased metabolic demand persisting beyond the FSE may contribute to the epileptogenesis.
Supported by NIH grant NS35439 and NS 078279

3.065
EFFECT OF VALPROIC ACID AND MTHFR C677T POLYMORPHISMS ON PLASMA HOMOCYSTEINE CONCENTRATIONS: IMPLICATIONS FOR VASCULAR DISEASE

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Rationale: Elevated plasma total homocysteine (tHcy) is an independent risk factor for developing vascular disease. We investigated the relationship between elevated tHcy concentrations, caused by both valproic acid (VPA) therapy, 5-methylenetetrahydrofolate reductase (MTHFR) genotype, and indirect measures of endothelial function in epileptic children and adolescents.
Methods: Patients with epilepsy treated with VPA and controls without epilepsy (VPA naïve) were recruited. Endothelial function was assessed via peripheral arterial tonometry (PAT) in all participants at baseline. Overnight fasting blood samples were obtained from the epileptic group to assess plasma tHcy, erythrocyte folic acid and serum vitamin B12 concentrations via high-performance liquid chromatography (HPLC) and core lab procedures, while MTHFR genotypes were determined via Genotype-specific Approaches to Therapy in Childhood (GATC) protocol. Serum samples provided from controls were used to assess serum tHcy concentration via HPLC. Within 6 months the same parameters were assessed again in the epileptic group.
Results: Nine epileptic patients (78% male; ages 7-16 years) and 31 controls (39% male; ages 11-16 years) were recruited. tHcy concentration significantly increased in epileptic patients after follow-up compared to controls (+29%; P=0.016) while vitamin B12 concentration demonstrated a trend towards a gradual decline. Epileptic patients expressing the 677CT genotype had elevated tHcy and reduced folic acid concentrations compared to patients expressing the 677CC genotype. Endothelial function was affected in epileptic patients, indicated by a significant reduction in the reactive hyperemia-PAT index at baseline and follow-up in epileptic patients compared to controls (-20%; P=0.018 and -23%; P=0.012, respectively), with a corresponding increase in tHcy and decrease in vitamin B12 concentrations.
Conclusions: This pilot study prospectively documents an association between elevated tHcy concentration and endothelial dysfunction assessed by PAT in children with diagnosed epilepsy expressing the MTHFR 677CT polymorphism when treated with