Epilepsy Research (2013) **107**, 224—230

journal homepage: www.elsevier.com/locate/epilepsyres

Modulation of excitability by continuous low- and high-frequency stimulation in fully hippocampal kindled rats

Joacir G. Cordeiro[a,b,c,*], **Karin H. Somerlik**[a,d], **Karina K. Cordeiro**[a,b], **Ad Aertsen**[d,e], **João C. Araújo**[c], **Andreas Schulze-Bonhage**[a,d]

[a] *Epilepsy Center, University Hospital Freiburg, Breisacherstrasse 64, 79106 Freiburg, Germany*
[b] *Department of Stereotaxic Neurosurgery, University Hospital Freiburg, University of Freiburg, Breisacherstrasse 64, 79106 Freiburg, Germany*
[c] *Department of Neurosurgery, Hospital de Clinicas, Federal University of Paraná, R: General Carneiro 181, 80060-900 Curitiba, Paraná, Brazil*
[d] *Bernstein Center Freiburg, University of Freiburg, Hansastrasse 9A, 79104 Freiburg, Germany*
[e] *Neurobiology and Biophysics, Faculty of Biology, University of Freiburg, Schaenzlestrasse 1, 79104 Freiburg, Germany*

Received 14 December 2011 ; received in revised form 20 July 2013; accepted 15 August 2013
Available online 19 September 2013

KEYWORDS
Kindling;
Hippocampus;
Low-frequency brain stimulation;
High-frequency brain stimulation;
Hippocampal stimulation;
Multi-site stimulation

Summary
Background: Low- and high-frequency stimulation (LFS and HFS, respectively) have been, reported to modify seizure characteristics in rats. We here report effects of hippocampal LFS and HFS, applied at two or four sites in fully kindled rats.
Methods: Rats were kindled through a hippocampal tetrode until the fully kindled state. Animals with, stable afterdischarge (AD) threshold were randomly assigned to 5 groups; stimulation at 1 Hz (LFS) or, 130 Hz (HFS) was continuously applied for 7 days at 2 or 4 intrahippocampal sites; a control, group received no stimulation. Four-contact stimulation was performed in a rotating fashion. Stimulation effects on AD threshold, AD duration and behavioral seizures were assessed.
Key findings: Four-contact LFS consistently increased AD threshold for a period of 2 days to 2 weeks, whereas 4-contact HFS significantly decreased AD duration 24 hours following the stimulation period. No significant AD modification was observed with either 2-contact stimulation paradigms. No, behavioral alteration occurred in any group.

* Corresponding author at: Breisacherstrasse, 64, D-79106 Freiburg im Breisgau, Germany. Tel.: +49 761 270 93020; fax: +49 761 270 93090.
E-mail addresses: joacir.cordeiro@uniklinik-freiburg.de, joacirgc@hotmail.com (J.G. Cordeiro).

0920-1211/$ — see front matter
http://dx.doi.org/10.1016/j.eplepsyres.2013.08.014

Significance: These findings suggest that effects of hippocampal stimulation depend on frequency and topography of stimulus application. LFS and HFS had anti-epileptic effect on afterdischarges when applied in a rotating pattern. This supports concepts on patterned stimulation to result in desynchronization and anti-kindling effects.

Introduction

Temporal lobe epilepsy (TLE) is the most common form of focal epilepsy in adults. The majority of cases is pharmacoresistant, therefore the mainstay of TLE treatment presently is the resection of the epileptogenic area (Volcy Gomez, 2004). Deep brain stimulation represents an alternative approach, but so far, its efficacy is lower than of resective procedures (Velasco et al., 2001, 2007; Boon et al., 2007; Vonck et al., 2007; Morrell, 2011).

Stimulus frequency appears to be an important parameter for effective seizure suppression (Mirski et al., 1997; Lado et al., 2003). Studies involving high-frequency stimulation (HFS) mainly used frequencies around 130 Hz (Boon et al., 2007; Osorio et al., 2005; Velasco et al., 2007). In addition, there have been experimental and clinical studies using low-frequency stimulation (LFS) paradigms of 1—5 Hz, based on the concept of induction of long-term depression (LTD) (Christie et al., 1994; Linden, 1994; Zhang et al., 2009; Sun et al., 2010). LFS animal data mainly derive from short-term stimulation paradigms (i.e. pre-emptive stimulation and quenching). This includes application in various experimental settings: LFS of in vitro slice preparations has been shown to induce long term depression (LTD), reducing excitability and elevating AD thresholds (Kemp and Bashir, 2001; D'Arcangelo et al., 2005). In vivo, Weiss et al. described the occurrence of LTD with LFS of the amygdala in kindled rats (Weiss et al., 1995, 1998). Also in human cortical slices, LTD was shown as a result of low frequency stimulation (Chen et al., 1996). Some clinical studies with limited patient numbers reported benefits of cortical LFS in patients with TLE (Tergau et al., 1999; Yamamoto et al., 2002; Vonck et al., 2002; Theodore and Fisher, 2004; Kinoshita et al., 2005; Schrader, 2006). Overall, long term depression of synaptic transmission has been established as a mechanism of plasticity which is not limited to the hippocampus and offers a strategy to reduce overexcitability in epilepsy (Bliss and Cooke, 2011).

Given the need to improve the efficacy of stimulation approaches compared to resective treatments, we performed a systematic study of different stimulation paradigms: at high and low frequency, via two and four electrode contacts on the epileptic focus in a rat hippocampal kindling model. Preliminary results were presented in abstract form (Cordeiro et al., 2010 *ESSFN* 2010; 8/OP29).

Methods

Animals were obtained through the University Medical Center Freiburg. All experimental procedures used in this study were performed in accordance to the Freiburg University and German guidelines for animal research and with authorization of the regulatory authorities. Thirty-seven female Wistar rats weighing 307 ± 14.5 g composed the experimental group and were housed in transparent plastic cages under a 12-hour light (day) and 12-hour darkness (night) cycle. Temperature was maintained at 21 ± 1 °C, humidity at 50—60% and food and water ad libitum. For the electrode implantation intraperitoneal anesthesia with ketamin/xylazine was applied, followed by post-operative analgesia with buprenorphin. After performing skin incision and skull burr holes, a quadripolar electrode of four twisted insulated platinum electrodes (Ø125 μm, 1 mm tip separation) was implanted in the right posterior hippocampus at stereotaxic coordinates AP = −5.5; M-L = +4.8; *V* = −7.0 referenced from bregma and skull surface (Paxinos and Watson, 2007). An insulated tungsten electrode was placed in each hippocampus for recording (Ø60 μm, AP = −4.0; M-L = ±2.6; *V* = −3.0), a reference electrode (same specifications) was placed 1 mm posterior to lambda 3 mm deep on the left and on the right, an epidural screw was connected with a low resistance cable for grounding. Electrodes were connected to the multichannel connector and the implant was fixed to the skull.

Placement control

Electrode positions were controlled in vivo using physiological criteria (wave shape and temporal profile of AD) and *post-mortem* using Nissl stains. Only rats that presented the typical hippocampal AD profile (primary AD, interval, rebound and ''wet dog shakes'') were selected for the study (McIntyre, 2006). Rats were perfused for histological assessment with intracardiac formalin solution under deep anesthesia. Coronal brain slices of 50 μm thickness were used for histological analysis. Placement was considered adequate when the electrode tips were inside the hippocampal limits. Additionally we controlled that no other morphologic alteration besides the electrode tracks were induced by the stimulation protocols.

Recording and stimulation setup

Activity recorded from the rat brain was sent from the MPA8I pre-amplifier (Multi Channel Systems, Reutlingen, Germany) and the slipring (Air Precision, Le Plessis-Robinson, France) to the PGA32 signal amplifier (Multi Channel Systems, Reutlingen, Germany). The PGA32 was coupled to an A-D converter (CED Power 1401, Cambridge Electronic Design, Cambridge, England). Recordings were amplified (×500), broad-band filtered (from 1 Hz to 5 kHz) and digitized at 10.4 kHz sampling rate, with simultaneous HD-video monitoring. The software Spike2 was used to display and register the output from the A-D converter. Two STG2008 stimulators, with eight independent channels each, were used for stimulation (Multi Channel Systems, Reutlingen, Germany).

Kindling was performed using supra-threshold bipolar stimulation at the inner contacts consisting of a 1.6 s

Table 1 Mean stimulation amplitude applied in the different groups for the one-week stimulation on two (2C) or four (4C) contacts.

	HFS-2C	HFS-4C	LFS-2C	LFS-4C
Stimulation amplitude (μA)	414 (±83)	233 (±55)	687 (±13)	700 (±0)

Stimulation amplitudes applied in LFS2C and LFS4C groups were statistically significantly higher than those applied in HFS2C and HFS4C groups, respectively ($p < 0.01$ in both comparisons). Data in μA ± 1 standard error.

stimulus train of biphasic rectangular pulses at 60 Hz. Each pulse lasted 0.4 ms and had amplitude of 0.5 mA. The stimulus train was applied daily in series of five consecutive days, separated by intervals of two days. In each stimulation session, the triggering of an afterdischarge by the suprathreshold stimulation was verified by the LFP recording. The process was continued until the rats reached behavioral seizures of degree five on the Racine scale (Racine, 1972) for 10 consecutive sessions (considered the fully kindled state). In each kindling session, recordings were performed for at least 150 s after the end of stimulus application.

AD threshold and stimulation protocols

Upon reaching the fully kindled state, the individual afterdischarge threshold (ADT) was determined. Stimulus amplitude was increased in steps of 25 μA from 0 to 100 μA and in steps of 50 μA from 100 to 800 μA (McIntyre, 2006). ADT was determined once daily across 3 consecutive days. Animals were considered stable when ADT remained unchanged or differed only one step across 3 consecutive days. Only stable animals were included in this study, and were randomly assigned into five groups. Randomization was performed sequentially distributing the offspring of individual rats assigning one animal per offspring to each of the five study groups with the aim to evenly distribute variability of genetic background.

After the third ADT measurement, each animal was submitted to treatment with continuous stimulation of the kindled hippocampus for 7 days. Stimulation amplitude was individually determined using the same ADT protocol. When either an electrographic or a behavioral alteration was observed, stimulation was ceased. For safety reasons, the amplitude used in each stimulation protocol (SP) was 100 μA less than AD threshold. Four different bipolar stimulation protocols with charge-balanced biphasic square-waves were applied:

- High-frequency stimulation via 2 contacts (HFS2C) group ($N = 7$) — HFS at 130 Hz, pulse width 80 μs, delivered at the outer contacts.
- Low-frequency stimulation via 2 contacts (LFS2C) group ($N = 8$) — LFS at 1 Hz, pulse width 120 μs, delivered at the outer contacts.
- High-frequency stimulation via 4 contacts (HFS4C) group ($N = 9$) — HFS at 130 Hz, pulse width 80 μs, delivered at the 4 pairs of contacts in rotating fashion (selection of electrode pairs switched after each pulse).
- Low-frequency stimulation via 4 contacts (LFS4C) group ($N = 7$) — LFS at 1 Hz, pulse width 120 μs, delivered at the 4 pairs of contacts in rotating fashion (selection of electrode pairs switched after each pulse).
- Control group ($N = 6$) — receiving no stimulation.

Statistically significant higher SP amplitudes could be applied to the LFS2C and LFS4C groups compared to those applied in HFS2C and HFS4C groups, due to the lack of electrophysiological and behavioral alterations (Table 1). During the 7 days of continuous stimulation no ADT determination and no recording was performed. On the 7th day, stimulation ended and ADT was determined at zero, 24 and 48 hours after stimulation end. Daily ADT measurement sessions before the SP (Pre1, Pre2 and Pre3) were compared to sessions performed after the SP (Post1, Post2 and Post3). Stability of the kindling model was asserted in the control group.

AD characterization and behavioral seizures

Recordings of ADT determination sessions were Fourier transformed to frequency spectrograms using the Matlab 6.5 software (MathWorks, Natick, USA). AD start was marked when the AD frequency content exceeded the frequency band of the epoch before the triggering stimulus (baseline). AD end was marked when the AD frequency content returned to baseline. This method was adopted to refine AD analysis according to earlier results on AD characterization through computational data processing (Cordeiro et al., 2010). The interval length between AD start and AD end was referred to as AD duration.

Behavioral seizure intensity was classified using the Racine scale. Behavioral seizure onset was marked on HD-video recordings when the animal reached Racine grade 3 or higher, the end was marked when motor phenomena were inferior to that grade.

Statistical analysis

Statistical analysis was performed according to the advice of the Department of Statistics from the University of Freiburg. Results are presented in means ± standard error (SE). AD threshold, AD and behavioral seizure duration were analyzed using the Sign Test at a significance level of 95% ($p < 0.05$). SP amplitude was compared across groups using the Mann—Whitney *U*-test at a significance level of 95% ($p < 0.05$). For analysis, the SPSS software was used (SPSS Inc., Chicago, USA).

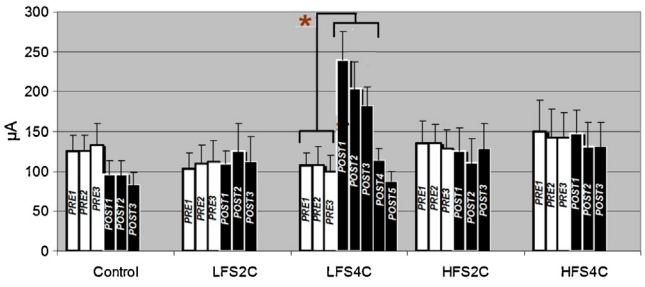

Figure 1 Mean afterdischarge threshold (ADT) in the different groups before and after one week of stimulation on two (2C) or four (4C) contacts. In the LFS4C group, Post1, Post2 and Post3 values were statistically significantly higher than the mean of Pre values (red star) ($p = 0.023$ for the three comparisons). The other groups showed no significant differences. Data in μA + 1 standard error.

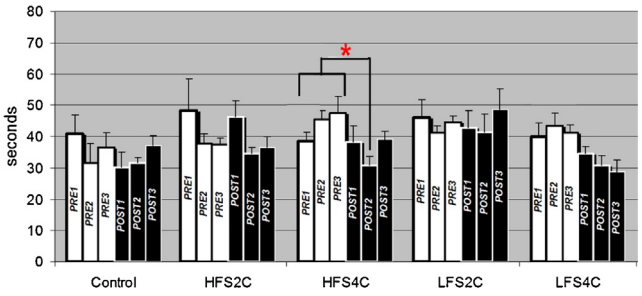

Figure 2 Mean afterdischarge duration (ADD) in the different groups before and after one week of stimulation on two (2C) or four contacts (4C). The HFS4C group showed a statistically significant decrease in ADD comparing values before and after stimulation (red star), with Post2 being shorter than the mean of Pre values ($p = 0.02$). No significant changes in ADD were observed in the other groups. Data in seconds + 1 standard error.

Results

Stimulation protocols and AD threshold

On average, the fully kindled state was achieved 75.6 ± 23.4 days after onset of kindling stimulation. In the LFS4C group, AD thresholds at post-treatment assessment on day one to three (Post 1, Post 2 and Post 3 values) were significantly higher than the mean of pre-treatment values ($p = 0.023$ for the three comparisons). As none of the animals of this group returned to Pre-SP ADT levels in Post3, they were re-tested one week later (Post4). In Post4, five out of seven animals returned to baseline ADT; the two animals with still persistently elevated AD were re-tested after another week (Post5), only one animal returned to Pre-SP ADT, the other persisted with higher ADT.

In HFS2C, LFS2C, HFS4C and control group differences between pre- and post-stimulation AD thresholds were not statistically significant (Fig. 1).

Afterdischarge duration

The HFS4C group revealed a statistically significant decrease in AD duration 24 hours after stimulation ending, with Post2 being shorter than the mean of Pre-SP values ($p = 0.02$). No significant changes in ADD were observed in the HFS2C, LFS2C, LFS4C and control groups (Figs. 2 and 3).

Behavioral seizure duration

No statistically significant differences were observed when comparing Pre and Post values regarding behavioral seizure intensity (typically Racine 5) and duration (typically around 30 s) of all, HFS2C, HFS4C, LFS2C, LFS4C and control groups (Table 2).

Discussion

We here report stimulation pattern-dependent effects of hippocampal HFS and LFS in the rat-kindling model. As electrical brain stimulation is increasingly considered as an alternative approach for medically refractory epileptic patients, who are not candidates for surgical resection of the epileptogenic area, stimulation of the epileptic focus is a particularly attractive approach to alter pathological local neural network dynamics. With focal hippocampal epilepsy, there is a particular interest for stimulation approaches in patients with bilateral independent seizure onsets and in patients considered at high risk of memory losses following resective surgery.

Several clinical studies with low patient numbers (≤10) have reported reductions in seizure rate using continuous

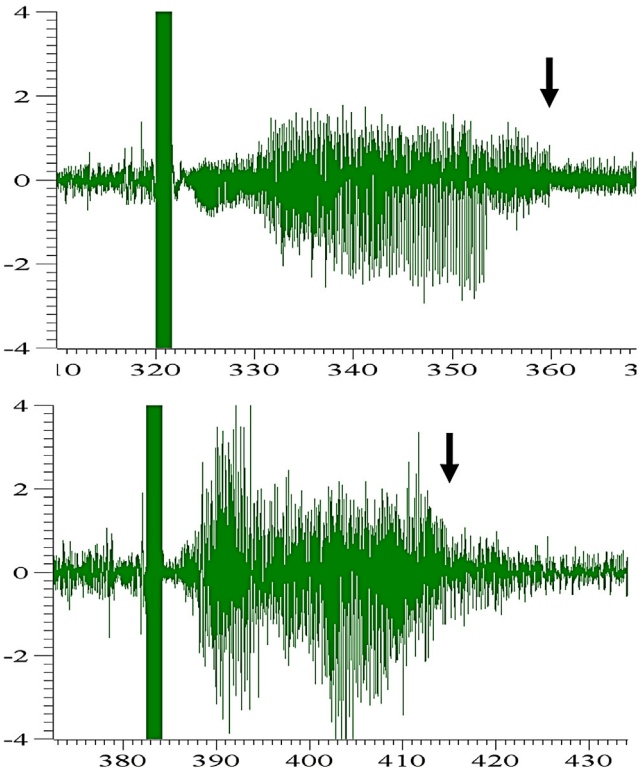

Figure 3 Representative LFP recording of two afterdischarges (AD) from a rat in the HFS-4C group, a Pre-SP (up) and a Post-SP (down) stimulation session. This case illustrates the AD duration decrease observed after one week of desynchronizing HFS. Black arrows indicate the AD end. Scale bars in mV and seconds.

Table 2 Behavioral seizure onset was marked when the animal reached Racine grade 3 or higher and the end when motor phenomena were inferior to that grade.

	PRE1	PRE2	PRE3	POST1	POST2	POST3	POST4	POST5
Control	26.7 (2.0) 5	28.8 (1.5) 5	27.0 (1.2) 5	27.6 (3.7) 5	31.2 (2.5) 5	30.4 (0.7) 5	x	x
LFS2C	28.1 (2.1) 5	27.9 (1.8) 5	26.0 (2.5) 5	33.1 (3.9) 5	24.4 (2.7) 5	30.5 (3.5) 5	x	x
LFS4C	27.2 (1.0) 5	27.7 (2.0) 5	29.0 (2.1) 5	29.5 (2.7) 5	29.3 (1.3) 5	28.8 (0.8) 5	31.8 (4.3) 4.7	31.5 (2.5) 5
HFS2C	26.7 (1.3) 5	25.7 (1.7) 5	29.4 (1.1) 5	30.7 (2.8) 5	30.8 (3.3) 5	29.5 (2.0) 5	x	x
HFS4C	34.1 (2.9) 5	33.4 (4.5) 5	31.7 (2.7) 5	26.8 (3.3) 5	33.3 (1.5) 5	39.0 (5.0) 5	x	x

Values demonstrating the mean duration and mean Racine grade of behavioral seizure of each group in each session. Duration shown in seconds (standard error) Racine grade.

hippocampal HFS (Boon et al., 2007; Osorio et al., 2005; Velasco et al., 2007); no cognitive side effects were noted. Recently, multicentre trials resulted in a reduction by 40.4% vs. 14.5% in a control group after 3 months of treatment with thalamic stimulation (Fisher et al., 2010), and in a reduction in seizure frequency by 41.5% vs. 9.4% with responsive focus stimulation (Morrell, 2011). LFS paradigms were investigated in clinical trials less extensively. A patient showed mild reduction of interictal epileptiform discharges after temporal cortical LFS (Yamamoto et al., 2002). Kinoshita et al. (2005) reported a spike reduction of 18.5% and a slight power decrease in the 12—14 Hz frequency band after cortical LFS of four patients.

Our study was designed to evaluate the importance of stimulus frequency and numbers of sites to be stimulated. In the groups where stimulation was delivered via two contacts (LFS2C, HFS2C), no significant changes were induced. By contrast, stimulation applied through four contacts (LFS4C, HFS4C) in a sequential order showed specific seizure suppressive effects. LFS applied via four contacts induced a significant increase in AD threshold by a factor of more than two. Moreover, this effect lasted for at least 2 days and in two animals even at least a week. By contrast, HFS applied over four contacts did not significantly increase AD threshold but shortened AD duration 24 hours after HFS interruption (Post2).

A seizure suppressive effect was more evident in the four-contact stimulation — this may be due to the alternate design of this stimulation paradigm. It was based on theoretical reports of long-term anti-kindling effects of desynchronizing brain stimulation (Tass and Majtanik, 2006). There, unlike permanent HFS, desynchronizing stimulation showed powerful long-term anti-kindling effects, enabling the network to unlearn pathologically strong synaptic interactions by disrupting the abnormally increased synchronicity of the pathological network. An alternative explanation would be that involvement of electrodes with a different spatial topography in relation to the seizure focus contributed to the improved antiepileptic effects of four-contact stimulation. Further studies will be necessary to further define such spatial dependency of stimulus application and to study if changes in the topography of applied electric fields or the timing of sequential stimulations are more critical in modulating the excitability of kindled areas.

Current theories to explain DBS effects suggest not only local alterations of neuronal activity: (1) HFS may induce a blockage of the voltage-dependent membrane ion channels of neurons adjacent to the stimulation (*depolarization block*) (Beurrier et al., 2001). (2) synaptically mediated inhibition of neurons may occur by antidromic activation of inhibitory afferences and GABA release (*GABAergic inhibition*) (Dostrovsky et al., 2000). (3) orthodromic excitation of efferent axons and inhibition of synaptic transmission in projection areas may occur by exhaustion of neurotransmitter pools (*synaptic depression*) (Zucker and Regehr, 2002). (4) neuronal activity may be masked by non-physiological high-frequency signaling (*jamming*) (Montgomery and Baker, 2000).

There is recent evidence of higher efficacy of HFS (130 Hz) in affecting excitability compared to LFS (5 Hz) with hippocampal stimulation in a rapid kindling model (Wyckhuys et al., 2010). AD threshold increased when ADs were elicited during continuous HFS, whereas AD duration was not relevantly influenced. LFS did neither affect AD threshold nor duration significantly. Differences between these results and the findings reported here may be related to the different kindling protocols and other stimulation techniques. We opted for the standard kindling, in which the fully kindled state was induced after 75.6 ± 23.4 days, whereas in the rapid kindling it was induced after 4 stimulation days. Moreover, electrode tips separation for kindling was 10 times larger in our experiments. We stimulated in a rotatory fashion. This allowed the application of considerably higher amplitudes, which may have contributed to the AD threshold increase. Both studies, however, suggest that frequency, amplitude and modus of stimulation are relevant factors in the modulation of excitability. Our study is well compatible with the concept that excitability can be decreased by network desynchronization promoted by functionally splitting the neuronal population into subpopulations (Tass and Majtanik, 2006). LFS at higher amplitude may have promoted a larger stimulation field and might, therefore, be more efficient in synchronizing neurons than HFS.

Electrical stimulation may induce synaptic plasticity in the form of short-term and long-term depression (Christie et al., 1994; Zucker and Regehr, 2002; Bliss and Cooke, 2011). LFS-induced LTD appears to be mediated by NMDA and calcium entry via voltage-sensitive channels and triggered by postsynaptic activation (Bear and Abraham, 1996; Christie et al., 1994). A number of secondary mechanisms are implied in its maintenance over prolonged periods of time (Bliss and Cooke, 2011). Whereas LFS has been shown to reduce interictal epileptic spiking both in vivo animal

models of epilepsy (Bragin et al., 2002), analyses of different settings of stimulus application, as performed here, may widen the therapeutic applicability of this stimulation technique. The modulation of GABA-BZD and endogenous opioid systems may also be involved in the effects of LFS (Lopez-Meraz et al., 2004). Whether LTD or depolarization block are the underlying mechanisms responsible for the anti-epileptic effect promoted by the desynchronizing LFS and HFS in our experiment remains to be established. Future experiments will need to assess the effects of continuous stimulation on local release of neurotransmitters, changes in receptor binding properties and/or receptor densities for those transmitters, as well as on changes in gene expression associated with the relatively long-lasting increases in local AD thresholds. Depending on these mechanisms, intermittent and/or aperiodic stimulation could be as efficacious as periodic continuous stimulation (Kumar et al., 2011).

In conclusion, continuous LFS could be applied safely in fully kindled rats and did not modify their behavior. Our findings suggest that continuous LFS may decrease the excitability of the focus in fully hippocampus kindled rats, and that multi-site stimulation paradigms may prove superior to stimulation at a fixed hippocampal site. Further studies are necessary to determine the possible benefits of continuous LFS applied to different epilepsy models, and on the use of continuous cyclic stimulation paradigms.

Acknowledgments

This work was supported by the German Federal Ministry of Education and Research (BMBF-01GQ0420 to Bernstein Center Computational Neuroscience (BCCN) Freiburg, BMBF-01GQ0830 to Bernstein Focus in Neurotechnology (BFNT) Freiburg/Tübingen) and the Deutscher Akademischer Austauschdienst (DAAD).

1) BMBF: Towards controlling pathological network dynamics - Terminating ictal epileptic activity by electrical stimulation of the epileptic focus. BCCN Freiburg, TP C3

2) BMBF: Multicontact stimulation techniques for interventions in human focal epilepsyBernstein Center for Neurotechnology, C5

3) DFG: Smart intervention techniques for in-vivo closed-loop stimulation in focal epilepsy. Excellence Cluster BrainLinks-BrainTools EX 1086.

This paper is a partial requirement for Cordeiro JG to acquire a PhD degree from the Federal University of Paraná with the advisement from Araújo JC. Authors would like to thank Dr. Graf from the department of statistics of the University of Freiburg for the support in the statistical analysis.

References

Bear, M.F., Abraham, W.C., 1996. Long-term depression in hippocampus. Annu. Rev. Neurosci. 19, 437—462.

Beurrier, C., Bioulac, B., Audin, J., Hammond, C., 2001. High-frequency stimulation produces a transient blockade of voltage-gated currents in subthalamic neurons. J. Neurophysiol. 85 (4), 1351—1356.

Bliss, T.V.P., Cooke, S.F., 2011. Long-term potentiation and long-term depression: a clinical perspective. Clinics 66 (S1), 3—17.

Boon, P., Vonck, K., De Herdt, V., et al., 2007. Deep brain stimulation in patients with refractory temporal lobe epilepsy. Epilepsia 48 (8), 1551—1560.

Bragin, A., Wilson, C.L., Engel Jr., J., 2002. Rate of interictal events and spontaneous seizures in epileptic rats after electrical stimulation of hippocampus and its afferents. Epilepsia 43 (Suppl. 5), 81—85.

Chen, W.R., Lee, S., Kato, K., Spencer, D.D., Shepherd, G.M., Williamson, A., 1996. Long-term modifications of synaptic efficacy in the human inferior and middle temporal cortex. Proc. Natl. Acad. Sci. U. S. A. 93 (15), 8011—8015.

Christie, B.R., Kerr, D.S., Abraham, W.C., 1994. Flip side of synaptic plasticity: long-term depression mechanisms in the hippocampus. Hippocampus 4, 127—135.

Cordeiro, J.G., Aertsen, A., Somerlik, K.H., Cordeiro, K.K., Araújo, J.C., Schulze-Bonhage, A., 2010. Evaluation of desynchronizing continuous low- and high-frequency stimulation in fully hippocampal kindled rats. In: XIX ESSFN Congress (8/OP29), p. 23.

D'Arcangelo, G., Panuccio, G., Tancrdi, V., Avoli, M., 2005. Repetitive low-frequency stimulation reduces epileptiform synchronization in limbic neuronal networks. Neurobiol. Dis. 19, 119—128.

Dostrovsky, J.O., Levy, R., Wu, J.P., Hutchison, W.D., Tasker, R.R., Lozano, A.M., 2000. Microstimulation-induced inhibition of neuronal firing in human globus pallidus. J. Neurophysiol. 84 (1), 570—574.

Fisher, R., Salanova, V., Witt, T., et al., 2010. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia 51, 899—908.

Kemp, N., Bashir, Z.I., 2001. Long-term depression: a cascade of induction and expression mechanisms. Prog. Neurobiol. 65, 339—365.

Kinoshita, M., Ikeda, A., Matsuhashi, M., et al., 2005. Electric cortical stimulation suppresses epileptic and background activities in neocortical epilepsy and mesial temporal lobe epilepsy. Clin. Neurophysiol. 116 (6), 1291—1299.

Kumar, A., Cardanobile, S., Rotter, S., Aertsen, A., 2011. The role of inhibition in generating and controlling Parkinson's disease oscillations in the basal ganglia. Front. Syst. Neurosci. 5, 86.

Lado, F.A., Velisek, L., Moshe, S.L., 2003. The effect of stimulation of the subthalamic nucleus on seizures is frequency dependent. Epilepsia 44, 157—164.

Linden, D.J., 1994. Long-term synaptic depression in the mammalian brain. Neuron 12, 457—472.

Lopez-Meraz, M.L., Neri-Bazan, L., Rocha, L., 2004. Low frequency stimulation modifies receptor binding in rat brain. Epilepsy Res. 59, 95—105.

McIntyre, D.C., 2006. The kindling phenomenon. In: Pitkänen, A., Schwartzkrion, PA., Moshé, SL (Eds.), Models of Seizures and Epilepsy. Elsevier Academic Press, San Diego, pp. 351—363.

Mirski, M.A., Rosell, L.A., Terry, J.B., Fisher, R.S., 1997. Anticonvulsant effect of anterior thalamic high frequency electrical stimulation in the rat. Epilepsy Rev. 28, 89—100.

Montgomery, E.B., Baker, K.B., 2000. Mechanisms of deep brain stimulation and future technical developments. Neurol. Res. 22 (3), 259—266.

Morrell, M.J., 2011. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. Neurology 77, 1295—1304.

Osorio, I., Frei, M.G., Sunderam, S., et al., 2005. Automated seizure abatement in humans using electrical stimulation. Ann. Neurol. 57 (2), 258—268.

Paxinos, G., Watson, C. (Eds.), 2007. The Rat Brain in Stereotaxic Coordinates. Elsevier Inc., Amsterdan.

Racine, R.J., 1972. Modification of seizure activity by electrical stimulation. II. Motor seizure. Electroencephalogr. Clin. Neurophysiol. 32, 281—294.

Schrader, L.M., 2006. Low frequency electrical stimulation through subdural electrodes in a case of refractory status epilepticus. Clin. Neurophysiol. 117, 781—788.

Sun, H.L., Zhang, S.H., Zhong, K., Xu, Z.H., Zhu, W., Fang, Q., Wu, D.C., Hu, W.W., Xiao, B., Chen, Z., 2010. Mode-dependent effect of low-frequency stimulation targeting the hippocampal CA3 subfield on amygdala-kindled seizures in rats. Epilepsy Res. 90, 83—90.

Tass, P.A., Majtanik, M., 2006. Long-term anti-kindling effects of desynchronizing brain stimulation: a theoretical study. Biol. Cybern. 94 (1), 58—66.

Theodore, W.H., Fisher, R.S., 2004. Brain stimulation for epilepsy. Lancet Neurol. 3, 111—118.

Tergau, F., Naumann, U., Paulus, W., Steinhoff, B.J., 1999. Low-frequency repetitive transcranial magnetic stimulation improves intractable epilepsy. Lancet 353, 220.

Velasco, A.L., Velasco, F., Velasco, M., Trejo, D., Castro, G., Carrillo-Ruiz, J.D., 2007. Electrical stimulation of the hippocampal epileptic foci for seizure control: a double-blind, long-term follow-up study. Epilepsia 48, 1895—1903.

Velasco, M., Velasco, F., Velasco, A.L., 2001. Centromedian-thalamic and hippocampal electrical stimulation for the control of intractable epileptic seizures. J. Clin. Neurophysiol. 18, 495—513.

Volcy Gomez, M., 2004. Mesial temporal lobe epilepsy: its physiopathology, clinical characteristics, treatment and prognosis. Rev. Neurol. 38, 663—667.

Vonck, K., Boon, P., Achten, E., De Reuck, J., Caemaert, J., 2002. Long-term amygdalohippocampal stimulation for refractory temporal lobe epilepsy. Ann. Neurol. 52, 556—565.

Vonck, K., Boon, P., Van Roost, D., 2007. Anatomical and physiological basis and mechanism of action of neurostimulation for epilepsy. Acta Neurochir. Suppl. 97 (Pt 2), 321—328.

Weiss, S.R., Li, X.L., Rosen, J.B., Li, H., Heynen, T., Post, R.M., 1995. Quenching: inhibition of development and expression of amygdala kindled seizures with low frequency stimulation. Neuroreport 13 (6), 2171—2176.

Weiss, S.R., Eidsath, A., Li, X.L., Heynen, T., Post, R.M., 1998. Quenching revisited: low level direct current inhibits amygdala-kindled seizures. Exp. Neurol. 154 (1), 185—192.

Wyckhuys, T., Raedt, R., Vonck, K., Wadman, W., Boon, P., 2010. Comparison of hippocampal Deep Brain Stimulation with high (130 Hz) and low frequency (5 Hz) on afterdischarges in kindled rats? Epilepsy Res. 88 (2—3), 239—246.

Yamamoto, J., Ikeda, A., Satow, T., et al., 2002. Low-frequency electric cortical stimulation has an inhibitory effect on epileptic focus in mesial temporal lobe epilepsy. Epilepsia 43, 491—495.

Zhang, S.H., Sun, H.L., Fang, Q., Zhong, K., Wu, D.C., Wang, S., Chen, Z., 2009. Low-frequency stimulation of the hippocampal CA3 subfield is anti-epileptogenic and anti-ictogenic in rat amygdaloid kindling model of epilepsy. Neurosci. Lett. 455, 51—55.

Zucker, R.S., Regehr, W.G., 2002. Short-term synaptic plasticity. Annu. Rev. Physiol. 64, 355—405.