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Effects of amygdala—hippocampal stimulation on interictal epileptic discharges

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Summary Deep brain stimulation (DBS) of different nuclei is being evaluated as a treatment for epilepsy. While encouraging results have been reported, the effects of changes in stimulation parameters have been poorly studied. Here the effects of changes of pulse waveform in high frequency DBS (130 Hz) of the amygdala—hippocampal complex (AH) are presented. These effects were studied on interictal epileptic discharge rates (IEDRs).

AH-DBS was implemented with biphasic versus pseudo monophasic charge balanced pulses, in two groups of patients: six with temporal lobe epilepsy (TLE) associated with hippocampal sclerosis (HS) and six with non lesional (NLES) temporal epilepsy.

In patients with HS, IEDRs were significantly reduced with AH-DBS applied with biphasic pulses in comparison with monophasic pulse. IEDRs were significantly reduced in only two patients with NLES independently to stimulus waveform.

Comparison to long-term seizure outcome suggests that IEDRs could be used as a neurophysiological marker of chronic AH-DBS and they suggest that the waveform of the electrical stimuli can play a major role in DBS. We concluded that biphasic stimuli are more efficient than pseudo monophasic pulses in AH-DBS in patients with HS. In patients with NLES epilepsy, other parameters relevant for efficacy of DBS remain to be determined.

Introduction

Mesial temporal lobe epilepsy (TLE) is often associated with pharmacoresistance. Resection of the epileptogenic zone, the primary treatment for pharmacoresistant mesial TLE, is not always possible. Depending on the epileptogenic zone localisation, surgical resection may impair crucial brain function such as memory or language. In these cases, deep brain stimulation (DBS) of the amygdala—hippocampal (AH) complex is a potential therapeutic technique. DBS is performed via intracranial depth electrodes and a neurostimulator. Unfortunately, there is minimal data concerning the effects of stimulation parameters on patient

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outcome other than stimulus frequency. The frequency of stimulation is the parameter that has been the most studied. Most studies use high frequencies (i.e. >100 Hz) known to be more efficient (Boëx et al., 2007). The effects of other parameters are less well known. Different waveforms have been applied in various studies, e.g. sinus waves (Goodman et al., 2005) or square waves (Weiss et al., 1998), without in-depth study of the effects that could be attributed to the use of different waveforms. Present neurostimulators use pseudo monophasic charge balanced pulses: a high amplitude, short duration and negative phase, precedes a low amplitude, long duration and positive phase (Butson and McIntyre, 2007). These neurostimulators are capacitively coupled to prevent neurotoxic effects due to residual charge that occurs with charge unbalanced pulses (McCreery et al., 1990). Nevertheless, charge balanced pseudo monophasic pulses may not be the safest stimuli to prevent tissue damage and biphasic pulses have been recognized as safer (Pudenz et al., 1975; Merrill et al., 2005). Up to now, the clinical effects of using pseudo monophasic or biphasic pulses, have never been addressed.

To predict and evaluate the stimulation efficacy of AH-DBS on seizure frequency, neurophysiological markers of stimulation effects are needed. Correlating interical epileptic discharge rates (IEDRs) with seizure frequency has been used previously to describe efficacy of vagal nerve (Koo, 2001; Olejniczak et al., 2001; Kuba et al., 2002), cortical (Kinoshita et al., 2005; Elisevich et al., 2006), thalamic centro-median nucleus (Velasco et al., 2001), and AH electrical stimulation. During AH electrical stimulation, decreases of IEDRs were assigned to decreases of seizure frequencies (Velasco et al., 2000) and increases of IEDRs were observed in conjunction with seizures for low frequency stimulation (Boëx et al., 2007). Thus, IEDRs can reflect the propensity of the brain to evolve into the seizure state.

The purpose of the present study was to analyze the effects of pseudo monophasic and biphasic, charge balanced pulses, applied with high frequency AH-DBS, in patients undergoing an invasive presurgical evaluation of their epilepsy, and in patients who received a neurostimulator for chronic AH-DBS. The effects were evaluated by the changes of IEDRs. They were analyzed independently in two groups of patients with TLE: one group with lesional and mesial TLE associated to hippocampal sclerosis (HS) and one group with non lesional TLE (NLES).

Methods

Patients

Twelve patients, six with non lesional (NLES) and six with lesional hippocampal sclerosis (HS, defined as increased FLAIR signal and reduced volume on T1-weighted MRI), all suffering from temporal lobe epilepsy (TLE), were enrolled in the present study during their invasive presurgical evaluation (eleven patients) or at the time they received a neurostimulator for chronic AH stimulation (three patients, two of them participated twice, Table 1). Intracranial invasive monitoring was offered because of the presence of conflicting scalp EEG data collected during non-invasive preoperative work-up. Stereotactic depth electrodes were implanted using a lateral to medial trajectory within the following structures: amygdala, anterior and posterior hippocampus, and frontal lobe. Patients were implanted with depth electrodes under stereotactic conditions (SD-8PX®, Ad-Tech Instruments, Racine, WI, USA) through an orthogonal approach. The drug treatment was tapered two to five days before study enrolment and kept constant in all patients. AH-DBS was evaluated at least twelve hours after the last seizure, to ensure that the effects of AH-DBS were measured from stable baselines of interictal activity with no residual effect of the previous seizure.

Three of these twelve patients received a chronic neurostimulator as treatment of their pharmacoresistant epilepsy for chronic AH-DBS (Pt7b, Pt8, Pt9). These patients participated in the study during the three days separating the implantation of the electrode and the internalization of the neurostimulator. The electrodes were implanted in the left temporal lobe with the Sub Compact Octad 3876 electrode (Medtronic Inc., Minneapolis, MN, USA). The drug treatment was not changed in all three patients during the study period. Two of these patients participated twice: initially during their invasive presurgical evaluation (S1, S6) and then at the time when they received their neurostimulator (Pt7b, Pt9, respectively).

Reconstruction of post-implantation high-resolution CT scans with pre-operative MRI allowed assessment of the position of the electrodes. A cerebral computed tomography (CT) was performed after implantation (slice thickness 1 mm). Co-registration with the patient's MRI using a 6 parameters rigid body algorithm enabled inter-modality registration in order to precisely assess the localisation of the depth electrode contacts (Pluim et al., 2003). Fig. 1 shows the postoperative MRI of patient S6-Pt9.

The research was conducted according to the recommended ethical guidelines of the Declaration of Helsinki and was approved by the Ethical Committee of the University Hospital of Geneva. All subjects gave informed consent.

Stimulation parameters

Stimulation was set at high frequency, 130 Hz that has been most often used in the field of AH-DBS and that did not show any seizure-provoking effects (Boëx et al., 2007; Boon et al., 2007; Velasco et al., 2007). Because the goal of the present study was not to analyze the effects of the frequency, it remained stable throughout the study. Charge balanced, bipolar electrical stimulation was applied to the estimated epileptogenic zone (i.e. the first contact involved in the patient's seizures).

Two stimuli of different waveforms were evaluated: (1) the standard pseudo monophasic and charge balanced pulses delivered by the Soletra neurostimulators (M37021, Medtronic Minneapolis, MN, USA), and (2) the biphasic charge balanced pulses delivered by the Grass S88X with the opto-isolator SIU-BI (Astro-Med, West Warwick, RI, USA). The phase width was 0.21 ms or 0.45 ms (given for each stimulation period in Table 2). It should be noted that with the Soletra neurostimulator, the reported phase width describes the cathodic (negative) phase of the pseudo monophasic pulse. The long width and low amplitude anodic (positive) phase is dependent on the phase width selected (Fig. 2).