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Assessing the equivalence between etomidate and seizure network dynamics in temporal lobe epilepsy

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HIGHLIGHTS

- Etomidate mimics some network properties of temporal lobe epilepsy seizures.
- Network temporal imbalance is reproduced during both etomidate administration and seizures.
- Etomidate effects could be used as a proxy for ictal dynamics in fMRI studies.

ABSTRACT

Objective: Etomidate mimics some typical epileptic neurophysiological features, such as the appearance of spikes and high frequency oscillations, when it is administrated to epileptic patients. However, little is known about its influence on the underlying cortical network. An assessment of comparable cortical dynamics between seizures and etomidate would allow for a more detailed study of the network parameters underlying the ictal stage by using etomidate as a proxy. The objective of the present work is to show that temporal lobe seizures produce network changes comparable to the ones elicited by etomidate administration.
Methods: Scalp and foramen ovale electrodes (FOE) recordings from nine temporal lobe epilepsy patients were analyzed under the complex network perspective. The clustering coefficients, average path lengths, density of links, modularity and spectral entropy were calculated during the pre-ictal and ictal stages and post-etomidate administration. Etomidate administration produced no seizure in any of the analyzed cases.
Results: The density of lines (six of nine patients) and spectral entropy (eight of nine patients) displayed similar behavior to the preictal–ictal transition when etomidate effects altered the epileptic network (FOE + scalp). When considering only the mesial sub-network, changes induced by etomidate perfusion replicated the same type of imbalance observed during the ictal stage in the nine patient's sample and in eight out of nine regarding the preictal stage. Both statistical significance at a level of 1% and size effects, evaluated by using the standardized mean differences, show similar network changes during the preictal–ictal and preictal–etomidate transitions.
Conclusions: Etomidate perfusion in patients with temporal lobe epilepsy induces network changes comparable to the changes resulting from seizures.
Significance: The finding reported here could improve the study of network dynamics during the ictal phase, not only with electrophysiological methods, but also in other cases, such as functional magnetic resonance imaging.

1. Introduction

Temporal lobe epilepsy (TLE) is the most common type of epilepsy and, fortunately, also has the best prognosis (de Tisi et al., 2011) for drug-resistant patients to whom surgery is the only curative/palliative alternative. In these subjects, careful and precise

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evaluation of each individual patient is mandatory to localize and define the essential minimum cortical zone to be resected during the surgery to eliminate or reduce the disabling seizures (Rosenow and Luders, 2001). This zone, called the epileptogenic zone (EZ), is in fact operationally defined because there is no diagnostic modality that can be used to determine its exact extent and location. If the patient is seizure free after the surgery, it must be concluded that the EZ was included in the resected cortex. The key element in this traditional approach to the treatment of drug-resistant temporal lobe epilepsy is in the effectiveness of the pre-surgical diagnostic tools and strategies employed to correctly localize the EZ. Neurophysiological (both invasive and non-invasive), structural and functional imaging tools are the most common diagnostic techniques currently used to localize the EZ. Pharmacological agents have also been used to improve accuracy in the pre-surgical diagnosis. Several types of drugs, including methohexital (Brockhaus et al., 1997), clonidine (Schmitt et al., 1999), pentylenetetrazol (Barba et al., 2007), thiopental (Kofke et al., 1993), and opiates (Manninen et al., 1999). However, non-specific responses often result, and poorly tolerated side-effects preclude the safe use of many drugs. Etomidate - a short-lived non-barbiturate imidazole derivative- acts onto the astrocytes in a specific way involving the GABA neurotransmitter system, what is extensively involved in epilepsy. In fact, it has been shown that etomidate can be safely used to activate epileptogenic activity (Krieger et al., 1985; Ebrahim et al., 1986; Gancher et al., 1984; Pastor et al., 2010; Stefan et al., 2010; Rampp et al., 2014). Although a few early studies suggested that etomidate administration may elicit seizures (Ebrahim et al., 1986; Gancher et al., 1984; Pastor et al., 2008a,b), a more recent and much larger study by Pastor et al. (2010) demonstrated that etomidate can be safely used to induce inter-ictal spiking activity ipsilateral to the seizure onset zone and can correctly lateralize 95% of patients with TLE, Moreover, etomidate induced epileptic activity has the potential to influence decisions regarding the placement of intracranial electrodes and the need for utilizing those type of electrodes (Pastor et al., 2010). Other studies have reported similar results for magnetoencephalography (Stefan et al., 2010) and high frequency oscillations (HFO) (Rampp et al., 2014). Though such approaches are important for the pre-surgical evaluation of drug-resistant TLE epilepsy patients, little is known about the effect of etomidate on the underlying functional networks in patients with epilepsy (Diessen et al., 2013). Until now, the application of network analysis on the ictal stage has provided valuable information regarding seizure onset, spread and termination (Ponten et al., 2007; Schindler et al., 2008; Kramer et al., 2010; Diessen et al., 2013), although it was almost exclusively based on the analysis of electrophysiological recordings. Due to the impeding challenges intrinsically associated with performing functional magnetic resonance imaging (fMRI) during seizures (patient safety, head motion, scanner access, etc.), new strategies that allow inferring ictal dynamics from fMRI studies will increases the current understanding of this pathology. Because etomidate intensifies typical epileptic features (spikes and HFOs) in a paroxysmal and time limited fashion, it could be used as a proxy for ictal activity, at least from a functional connectivity perspective. A thorough study of network dynamics during etomidate administration would facilitate a better understanding of epilepsy dynamics, specifically during the ictal and post-ictal stages.

The objective of this work is to show that etomidate administration, without eliciting ictal activity, produces changes in the underlying epileptic network in the same direction as the ones appearing during spontaneous seizures. The global and mesial characteristics were analyzed separately in nine drug-resistant TLE patients. From the global perspective (scalp and mesial network), we show that etomidate, without eliciting clinical seizures, produces comparable changes in two representative parameters (Boccaletti et al., 2006; Sporns et al., 2004): the density of links (DoL) and spectral entropy (SE), in a similar fashion as the changes appearing during the pre-ictal–ictal transition. Seizures and etomidate increase the synchronization of the whole network and increase the number of links between the recorded areas. Furthermore, SE, which is highly sensitive to anesthetic effects (Lallemand et al., 2004) and ictal activity (Kumar, 2008) behaves in a similar manner during both seizures and etomidate. In regard the mesial sub-networks, we show that etomidate mimics the synchronization imbalance appearing during seizures, a fact which was previously reported only during the inter-ictal stage (Bettus et al., 2009; Pereira et al., 2010; Ortega et al., 2010). To accomplish this task, we analyzed recordings from foramen ovale electrodes (FOE).

2. Methods

2.1. Neurophysiological data

A total of nine patients (5 women) were included in this study (Table 1). The mean age and duration of these intractable epilepsies were 37.77 ± 9.56 and 24.66 ± 13.74 years, respectively. This research was approved by the Ethical Committee of the Hospital de la Princesa. Informed consent was obtained from all patients. The patients were evaluated pre-surgically according to La Princesa's protocol, as previously published (Pastor et al., 2005; Sola et al., 2005). Briefly, all patients were studied with interictal single photon emission computer tomography (SPECT), using ^{99m}Tc-HmPAO (General Electric, Fairfield, CT, USA), magnetic resonance imaging (MRI) 1.5 T, (General Electric, Fairfield, CT, USA) with a specific protocol for epilepsy, 19 electrodes scalp EEG and video-EEG (XLTEK, Oakville, ON, Canada) with 19 scalp electrodes according to the international 10–20 system, complemented with FOE. In Table 1, we present the clinical information and results of the pre-surgical studies, such as SPECT, MRI and v-EEG, performed in patients with TLE. During the v-EEG recordings, antiepileptic drugs were progressively removed from the second day to the fourth day (approximately one third of the dose per day). We also included the overall physician diagnosis regarding lateralization. When the surgery was performed, the type of surgery and outcome (Engel scale) (Engel, 1993) are also included. Patients not requiring resective surgery were categorized as Engel scale 0.

Six-contact platinum FOEs with 1-cm center-to-center spacing (AD-Tech, Racine, USA) were inserted bilaterally under general anesthesia (Wieser and Schwarz, 2001; Pastor et al., 2008a,b). Correct implantation was assured by using fluoroscopic imaging in the operating room. We designated FOE1 as the most rostral electrode in the foramen ovale and FOE6 as the most occipital one. The left FOEs are designated as LFOE1, LFOE2, etc., and the right FOEs are designated as RFOE1, RFOE2, etc.

2.2. Etomidate administration and data analysis

Etomidate (Janssen-Cilag, Madrid, Spain) was intravenously administered (0.1 mg/kg) under quiescent conditions with the patient resting in the supine position in bed under continuous supervision by an experienced anesthesiologist. Supplementary oxygen was administered through nasal prongs at 5 L/min. The electrocardiogram (ECG), capillary oxygen saturation (SaO2), and respiratory rate (RR) were monitored continuously during the entire procedure (Pastor et al., 2008a,b, 2010). Zero time ($t = 0$) was defined as the time when drug perfusion was complete. None of the nine analyzed patients suffered from an etomidate induced seizure.