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Etomidate activates epileptic high frequency oscillations

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HIGHLIGHTS

- Etomidate increases the rate of interictal epileptic activity, including spikes and high frequency oscillations.
- Etomidate does not induce additional epileptic activity distinct from spikes or HFO seen without etomidate.
- Low frequency oscillatory activity triggered by etomidate does not show an association with spike and HFO distribution.

ABSTRACT

Objective: The short acting anesthetic etomidate has been shown to provoke epileptic spikes and rarely seizures. Influence of etomidate on the occurrence of epileptic HFO (high frequency oscillations) however is unknown. An HFO inducing effect of etomidate would allow further validation of the substance as a provocation measure in presurgical evaluation as well as provide insights into the common mechanisms of HFO, spike and seizure generation.
Methods: We retrospectively analyzed EEG data from four patients who underwent etomidate activation during invasive video-EEG monitoring with subdural strip electrodes. Spikes were manually selected in raw data, HFO in band pass filtered data (80–250 Hz). Rate and spatial distribution of HFO and spikes in three segments were compared: immediately after etomidate administration, as well as during slow wave sleep and while awake.
Results: Rates of HFO and spikes increased significantly after etomidate administration: Overall average rates of spikes were 9.7/min during sleep, 10/min while awake and 61.4/min after etomidate. Average HFO rates were 9.5/min during sleep, 8.3/min while awake and 24.4/min after etomidate ($p < 0.001$, non-parametric ANOVA). Spatial distributions of HFO and spikes after administration of etomidate were consistent with the seizure onset zone (SOZ) and area of resection when available (SOZ: two patients; resection: one patient; no information: one patient). Except for spurious events, no additional HFO and spike foci were seen with activation.
Conclusions: Etomidate administration activates spikes and HFO. Spatial distributions do not extend beyond electrodes showing spikes and HFO without Etomidate and seem consistent with the epileptic network.
Significance: Etomidate activation is a safe procedure to provoke not only epileptic spikes but also HFO, which were shown to have a high specificity for the SOZ.

1. Introduction

Epilepsy surgery requires exact evaluation of a patient's individual condition. Crucial to the viability of surgical therapy is the localization of the epileptogenic network in relation to essential functional areas (Cascino 2004; Rosenow and Lüders 2001).

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A spectrum of methods is applied to gather this information: While imaging may demonstrate structural correlates, only neurophysiological investigations like electro- or magnetoencephalography (EEG/MEG) and invasive EEG (iEEG) are able to prove pathophysiological involvement and yield information about the functional origin of epileptic activity. Functional investigations are especially valuable to evaluate propagation and connectivity within an epileptic network (Stefan and Lopes da Silva 2013).

Seizure activity, spikes and sharp waves are the electrophysiological targets of such investigations and constitute the markers of epileptic networks in clinical routine. In recent years, high frequency oscillations (HFO) have been recognized as an additional, highly specific marker of epileptogenic areas (Staba et al. 2002; Bragin et al. 1999). While the classification of HFO is still being discussed, there is evidence that oscillations between 250–500 Hz (“fast ripple”), 80–250 Hz (“ripples”) and 60–100 Hz (“high gamma”) represent distinct entities of fast activity with different degrees of association with epileptogenic networks: Slower oscillations demonstrate a more widespread spatial distribution with a less clear but present concentration in epileptogenic areas compared to fast ripples (Jacobs et al. 2008; Rampp et al. 2010; Worrell et al. 2004). A practical downside of HFO is, that they can only be reliably recorded using invasive EEG, although recent studies show preliminary evidence that non-invasive methods may be able to detect HFO (Xiang et al. 2009a; Xiang et al. 2009b; Rampp et al. 2010; Andrade-Valenca et al. 2011).

In patients with rare epileptic events, presurgical workup may be ineffective and possibly beneficial surgery is delayed. Longer recording durations to record sufficient activity are viable only to a limited degree due to the ensuing burden for the patient, as well as for financial and logistical reasons. For intraoperative electrocorticography during epilepsy surgery, considerably longer recording durations are no option at all. Typical procedures to provoke epileptic activity are tapering of anti-epileptic drugs (AED) and sleep deprivation. Furthermore, pharmacological agents can be administered to increase the quantity of epileptic activity and probability of seizures. Clonidine (Kettenmann et al. 2005) and dexmedetomidine (Mason et al. 2009) induce spike and sharp-wave activity, possibly by post-synaptic α_1- and α_2-receptor mediated attenuation of central noradrenergic transmission and depletion of central norepinephrin reduction of central norepinephrin lowers seizure thresholds (Mason et al. 2009), which may consequently also result in increased interictal epileptic activity. Barbiturates and derivatives are $GABA_A$-receptor agonists and thus mainly enhance GABA-inhibition. However, it has been shown, that e.g. thiopental and methohexital also lower excitation thresholds and increase epileptic activity. This effect is clinically utilized for intraoperative electrocorticography during epilepsy surgery (Wyler et al. 1987). Next to barbiturates, opioids, e.g. remifentanil, may be used to provoke epileptic activity in this context (Wass et al. 2001). Among other effects, remifentanil inhibits GABAergic interneurons, which inhibit excitatory neurons under normal circumstances, e.g. neurons involved in the generation of epileptic activity. This disinhibition of excitation may consequently result in an increase of epileptic activity (Siggins et al. 1986).

Intravenous administration of low-dose etomidate has been suggested as a further alternative activation approach. Few early reports have suggested that etomidate may provoke epileptic activity (Ebrahim et al. 1986; Gancher et al. 1984; Hsieh et al. 1990), but were not followed by larger studies. Pastor et al. have recently demonstrated in a case report that etomidate may trigger seizures, which they applied for ictal single photon emission tomography (SPECT) (Pastor et al. 2008). In a larger study, they showed that the substance may be safely used to induce interictal spiking activity, which they observed in all 20 investigated patients. In contrast, induced seizures were seen in only two patients (Pastor et al., 2010). The activated spikes, recorded by scalp EEG and invasive foramen ovale electrodes correctly lateralized the side of seizure onset in all but one patient.

In contrast, influence of etomidate on the occurrence of epileptic HFO is unknown. An HFO inducing effect of etomidate would allow further validation of the substance as a provocation measure, e.g. in patients with rare spontaneous activity. In situations with time constraints, e.g. in studies using MEG for non-invasive detection of HFO or intraoperatively for HFO-tailoring of resection extents (Wu et al., 2010), the ability to trigger HFOs would be beneficial. Furthermore, etomidate is used as an anesthetizing agent in the etomidate speech and memory test (“eSAM”) as an

Table 1
Clinical data.

Patient	1	2	3	4
Sex	Female	Male	Male	Female
Age	28	42	52	22
MRI	Normal	Cyst and gliosis left fronto-polar (DD: posttraumatic/post-inflammatoric defect, cortical dysplasia, ganglioglioma)	Hippocampal sclerosis right	Hippocampal sclerosis left
Interictal surface EEG	Temporo-mesial right and temporal neocortical	Frontal close to midline, left frontal	Fronto-temporo-mesial right, few spikes left temporal	–
Ictal surface EEG	Unclear, bilateral seizure onset	Unclear	Unclear	Left-fronto-temporal
Interictal invasive EEG	Temporo-basal/mesial right and temporopolar left	Diffuse (left and right frontal, bilateral frontal)	Temporo-basal and mesial right (mesial became apparent after addition of foramen ovale electrodes), few spikes left temporal	Left temporo-mesial and -basal
Ictal invasive EEG	Unclear	Bifrontal onset, enhancement of the left side	Temporo-mesial right	Left temporo-mesial
Ictal SPECT	Right hippocampus	Unclear	–	
FDG-PET	Right temporal (polar and mesial)	–	–	
Neuro-psychology	Left temporal	Left frontal	Right temporal/parietal, left temporo-lateral	Left temporal
Surgery	–	–	Hippocampal resection and anterior 2/3 of the temporal lobe on the right side. Several seizures in the first 3 months after surgery, then seizure free for 2 years up to now (Engel 2B, Wieser 1)	–
Histology	–	–	Hippocampal sclerosis	–