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Electroencephalogram signatures of ketamine anesthesia-induced unconsciousness

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HIGHLIGHTS

- Slow-delta oscillations that alternate with gamma oscillations (gamma burst) occur with ketamine at general anesthesia levels.
- Gamma, theta and decreased alpha/beta oscillations are not unique to ketamine at general anesthesia levels.
- The gamma burst pattern may result from circuit disruptions in cortical and subcortical sites.

ABSTRACT

Objectives: Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist commonly administered as a general anesthetic. However, neural circuit mechanisms to explain ketamine anesthesia-induced unconsciousness in humans are yet to be clearly defined. Disruption of frontal–parietal network connectivity has been proposed as a mechanism to explain this brain state. However, this mechanism was recently demonstrated at subanesthetic doses of ketamine in awake-patients. Therefore, we investigated whether there is an electroencephalogram (EEG) signature specific for ketamine anesthesia-induced unconsciousness.
Methods: We retrospectively studied the EEG in 12 patients who received ketamine for the induction of general anesthesia. We analyzed the EEG dynamics using power spectral and coherence methods.
Results: Following the administration of a bolus dose of ketamine to induce unconsciousness, we observed a "gamma burst" EEG pattern that consisted of alternating slow-delta (0.1–4 Hz) and gamma (~27–40 Hz) oscillations. This pattern was also associated with increased theta oscillations (~4–8 Hz) and decreased alpha/beta oscillations (~10–24 Hz).
Conclusions: Ketamine anesthesia-induced unconsciousness is associated with a gamma burst EEG pattern.
Significance: The EEG signature of ketamine anesthesia-induced unconsciousness may offer new insights into NMDA circuit mechanisms for unconsciousness.

1. Introduction

Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist that is used as a dissociative anesthetic (Domino et al., 1965; Corssen and Domino, 1966), a research model for schizophrenia (Insel, 2010), and a fast acting treatment for major depressive disorder (Zarate et al., 2006). At low doses, ketamine produces a dissociative state characterized by hallucinations, altered sensory perception and analgesia, while at higher doses it induces a state of unconsciousness appropriate for general anesthesia. For instance, an intravenous induction dose of ketamine (1–2 mg/kg) causes a rapid loss of consciousness that typically lasts for

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approximately 10 minutes (White et al., 1985; Vuyk et al., 2015). The use of ketamine as a general anesthetic in clinical practice is commonplace. For instance, during the recent propofol drug shortage in the United States, ketamine was one of the few alternative agents available for the induction of general anesthesia. However, we do not yet understand the neural circuit mechanisms to explain ketamine anesthesia-induced unconsciousness, and we lack principled neurophysiological signatures that could be used to monitor the brain during ketamine anesthesia-induced unconsciousness.

At the receptor level, ketamine blocks excitatory NMDA receptors on fast-spiking cortical interneurons more effectively than those on pyramidal neurons. This results in down regulation of inter-neuron activity, and decreased gamma amino-butyric acid (GABA) release at the interneuron–pyramidal neuron synapse (Homayoun and Moghaddam, 2007; Seamans, 2008). This decrease in inhibitory tone (decreased GABA release) results in markedly excited pyramidal neurons. This explains why ketamine is associated with increased cerebral glucose utilization and blood flow (Langsjo et al., 2004, 2005), and increased electroencephalogram (EEG) gamma oscillations (Ferrer-Allado et al., 1973; Schwartz et al., 1974; Schultz et al., 1990; Engelhardt et al., 1994; Hering et al., 1994; Lee et al., 2013; Blain-Moraes et al., 2014). Thus, the neurophysiological profile observed during ketamine-induced unconsciousness, which is suggestive of an active brain, is perplexing and remains a subject of intense interest in neuroscience.

Induction and maintenance of general anesthesia is associated with morbidity and mortality risks (Arbous et al., 2005; Cottrell, 2008). Therefore, human volunteer research studies of ketamine at general anesthesia levels are limited and challenging. However, an emerging paradigm to understand better the mechanisms of anesthetic action is to study EEG recordings obtained during routine clinical care, and relate neurophysiological findings to the behavioral state encountered and putative neural circuit mechanisms. We have found that this approach is effective for providing key insights into the mechanisms of anesthetic action (Akeju et al., 2014; Purdon et al., 2015a; Pavone et al., 2016).

Therefore, we retrospectively studied the EEG ($n = 12$) during unconsciousness induced by ketamine using spectral and coherence analysis methods. We report that ketamine anesthesia-induced unconsciousness defined by the behavioral state of unresponsiveness to verbal and tactile stimuli is associated with a characteristic gamma burst pattern (slow oscillations alternating with gamma oscillations), and we relate this pattern to cat neurophysiological experiments to suggest that the gamma burst pattern is a thalamocortical rhythm.

2. Materials and methods

2.1. Patient selection and data collection

The Human Research Committee at Massachusetts General Hospital approved this retrospective observational study. We reviewed our database of general anesthesia and simultaneous EEG recordings collected between September 1, 2011 and December 1, 2015. We identified 12 cases with baseline EEG recordings and ketamine (10 mg/mL; Bioniche Pharma, Lake Forest, IL) administration as the sole hypnotic agent for induction of general anesthesia. The EEGs of the 12 subjects were each reviewed for spectral artifacts and noise, and based on chart review, none of the patients had neurological or psychiatric abnormalities that could have interfered with the EEG.

Frontal EEG data were recorded using the Sedline brain function monitor (Masimo Corporation, Irvine, CA). The EEG data were recorded with a pre-amplifier bandwidth of 0.5–92 Hz, sampling rate of 250 Hz, with 16-bit, 29 nV resolution. The standard Sedline Sedtrace electrode array records from electrodes located approximately at positions Fp1, Fp2, F7, and F8, with ground electrode at Fpz and reference electrode approximately 1 cm above Fpz. Electrode impedance was less than 5 kΩ in each channel.

For all 12 patients, we selected EEG data segments by matching information from the electronic anesthesia record (Metavision, Dedham, MA) to the EEG and further confirmed the match by EEG analysis in the spectral domain (i.e. onset of anesthetic vapor on the electronic anesthesia record was manifest on the EEG by large power in slow, alpha and beta frequency bands). The electronic medical record was used to confirm ketamine as the sole hypnotic agent administered (isoflurane, sevoflurane, desflurane and nitrous oxide were not co-administered). Prior to the induction of general anesthesia with a bolus dose of ketamine, midazolam ($n = 8$; mean ± standard deviation; 1.8 ± 0.5 mg) and/or fentanyl ($n = 9$; 183 ± 79 mcg) were administered for anxiolysis and to block the sympathetic response to laryngoscopy, respectively. General anesthesia was induced with ketamine (mean ± standard deviation; 176 ± 32 mg) and intubation was carried out using succinylcholine, cisatracurium, or rocuronium for muscle relaxation. The gamma burst epochs were obtained 131 ± 86 seconds after the induction of general anesthesia, while the beta/gamma stable epochs were obtained 467 ± 106 seconds after the induction of general anesthesia. We defined gamma burst as gamma-oscillations that were interrupted by slow-delta oscillations, and beta/gamma stable as beta/gamma oscillations that were not interrupted by slow-delta oscillations. Given the doses of ketamine administered, and the underlying pharmacokinetic and pharmacodynamic properties of ketamine (Vuyk et al., 2015), we infer that the plasma levels of ketamine during the gamma burst were at therapeutic levels for unconsciousness, while the plasma levels of ketamine during the beta/gamma stable pattern were transitioning from therapeutic to sub-anesthetic levels.

Table 1 summarizes the patient characteristics and co-administered medications. Immediately prior to muscle relaxation and airway instrumentation, the patients ($n = 12$) did not respond to both verbal commands and lash reflex. During this period, the EEG was noted to be in the gamma burst pattern by time domain visualization. For all epochs analyzed, general anesthesia was maintained by the induction dose of ketamine previously administered. That is, no other anesthetics were administered during the gamma burst and beta/gamma stable epochs.

2.2. Spectral analysis

For each patient, we computed the power spectrum and spectrogram using multitaper spectral methods implemented in the Chronux toolbox (Percival and Walden, 1993). To obtain estimates of power spectra that are robust to noise and artifacts, we derived an EEG electrode that equally weighted the signals obtained from Fp1, Fp2, F7 and F8 (average of all four channels). The parameters for the multitaper spectral analysis were: window length $T = 2$ seconds with no overlap, time-bandwidth product TW = 3, number of tapers $K = 5$, and spectral resolution of 3 Hz. We also computed group-level spectrograms by taking the median across all patients. We did not normalize the EEG power, rather we computed the absolute power. We calculated the median spectra and 95% confidence intervals using a bootstrap procedure. Bootstrap samples for the spectrum were drawn from the full sample of data, consisting of all non-overlapping 2 second EEG windows for each subject. We computed the median spectrum across subjects and repeated this procedure 10,000 times to obtain bootstrapped spectral estimates of the median.