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$GABA_A$ circuit mechanisms are associated with ether anesthesia-induced unconsciousness

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HIGHLIGHTS

- Large amplitude slow oscillations, frontally coherent theta oscillations and frontally coherent alpha oscillations occur during general anesthesia induced with modern day derivatives of ether (MDDE).
- Reduction of GABAergic inhibitory post-synaptic potentials with ketamine resulted in beta/gamma (13–40 Hz) oscillations and significantly reduced MDDE anesthesia-induced slow, theta and alpha oscillation power.
- $GABA_A$ circuit-level mechanisms are associated with MDDE anesthesia-induced unconsciousness.

ABSTRACT

Objective: An emerging paradigm for understanding how anesthetics induce altered arousal is relating receptor targeting in specific neural circuits to electroencephalogram (EEG) activity. Enhanced gamma amino-butyric acid A ($GABA_A$) inhibitory post-synaptic currents (IPSCs) manifest with large-amplitude slow (0.1–1 Hz) and frontally coherent alpha (8–12 Hz) EEG oscillations during general anesthesia. Therefore, we investigated the EEG signatures of modern day derivatives of ether (MDDE) anesthesia to assess the extent to which we could obtain insights into MDDE anesthetic mechanisms.
Methods: We retrospectively studied cases from our database in which patients received isoflurane anesthesia vs. isoflurane/ketamine anesthesia ($n = 10$ each) or desflurane anesthesia vs. desflurane/ketamine anesthesia ($n = 9$ each). We analyzed the EEG recordings with spectral power and coherence methods.
Results: Similar to known $GABA_A$ circuit level mechanisms, we found that MDDE anesthesia induced large amplitude slow and frontally coherent alpha oscillations. Additionally, MDDE anesthesia also induced frontally coherent theta (4–8 Hz) oscillations. Reduction of GABAergic IPSCs with ketamine resulted in beta/gamma (13–40 Hz) oscillations, and significantly reduced MDDE anesthesia-induced slow, theta and alpha oscillation power.
Conclusions: Large amplitude slow oscillations and coherent alpha and theta oscillations are moderated by ketamine during MDDE anesthesia.
Significance: These observations are consistent with the notion that $GABA_A$ circuit-level mechanisms are associated with MDDE anesthesia-induced unconsciousness.

1. Introduction

Modern-day derivatives of ether (MDDE; desflurane, isoflurane, sevoflurane) are the principal inhalational anesthetic drugs administered for general anesthesia to enable the safe and humane conduct of traumatic surgical and diagnostic procedures (Campagna

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et al., 2003). Despite considerable progress in anesthesiology care and research, neural circuit mechanisms to explain MDDE anesthesia-induced unconsciousness are yet to be defined. However, an emerging paradigm for probing anesthetic mechanisms is to study electroencephalogram (EEG) recordings and relate the findings to the behavioral state and putative neural circuit-level mechanisms (Ching et al., 2010; Cimenser et al., 2011; Supp et al., 2011; Purdon et al., 2013, 2015a; Vijayan et al., 2013; Akeju et al., 2014a,b, 2015; Blain-Moraes et al., 2014; Pavone et al., 2016). This approach is beginning to provide key insights into the mechanisms of anesthetic agents.

Molecular studies of MDDE anesthetics have characterized actions at many receptor targets including gamma amino-butyric acid (GABA) A receptors (GABAr), acetylcholine receptors, glycine receptors, hyperpolarization-activated cyclic nucleotide-gated channels (HCN), N-methyl-D-aspartate receptors (NMDAr), potassium channels, serotonin receptors, and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic (AMPA) receptors, amongst others (Campagna et al., 2003; Rudolph and Antkowiak, 2004; Hemmings et al., 2005; Franks, 2006, 2008 Alkire et al., 2008; Brown et al., 2011). Among these molecular targets, GABAr agonism and NMDAr antagonism are two principal receptor level targets that have been proposed to explain MDDE anesthesia-induced unconsciousness (Campagna et al., 2003; Rudolph and Antkowiak, 2004; Hemmings et al., 2005; Franks, 2008). However, despite extensive molecular and *in vivo* studies, it is not well defined in humans, the extent to which GABAr agonism and NMDAr antagonism mediates MDDE anesthesia-induced unconsciousness. We have recently found that the EEG oscillations observed during sevoflurane anesthesia-induced unconsciousness are similar to those observed during propofol anesthesia-induced unconsciousness (Akeju et al., 2014b).

Propofol binds to the GABAr and potentiates chloride mediated inhibitory post synaptic currents (IPSCs) (Hales and Lambert, 1991). At surgical anesthetic depth, potentiation of GABAergic IPSCs manifests with large-amplitude slow oscillations (0.1–1 Hz) and coherent frontal alpha oscillations (8–12 Hz) (Gugino et al., 2001; Feshchenko et al., 2004; Leslie et al., 2009; Ching et al., 2010; Cimenser et al., 2011; Supp et al., 2011; Lewis et al., 2012; Mhuircheartaigh et al., 2013; Purdon et al., 2013; Vijayan et al., 2013; Akeju et al., 2014a,b). More recently, biophysical modeling studies have proposed a $GABA_A$ mediated thalamocortical mechanism for propofol anesthesia-induced frontal alpha oscillations (Ching et al., 2010; Cimenser et al., 2011; Purdon et al., 2013; Vijayan et al., 2013). Evidence that GABAergic inhibition may be the primary mechanism of MDDE anesthetic action is suggested by similar oscillations observed in the EEG during general anesthesia maintained with MDDE to those observed with propofol (Akeju et al., 2014b; Brown et al., 2015; Pavone et al., 2016).

Based on our clinical experience with the EEG and a synthesis of prior works, we can readily test GABAergic predictions for MDDE anesthesia circuit level mechanisms. We predict that during general anesthesia, MDDE like propofol should produce large amplitude slow and frontal alpha oscillations, which are largely dependent upon inhibition of pyramidal neurons in the cortex (Ching et al., 2010; Purdon et al., 2013; Vijayan et al., 2013; Akeju et al., 2014a,b). Presynaptic inhibition of these pyramidal neurons is accomplished by cortical interneurons (Homayoun and Moghaddam, 2007; Seamans, 2008). Since ketamine down-regulates interneuron activity and inhibitory tone, we also predict that ketamine would diminish MDDE anesthesia-induced alpha and slow oscillations.

Therefore, we retrospectively studied the EEG during isoflurane anesthesia- and desflurane anesthesia-induced unconsciousness with and without ketamine co-administration. We report that similar to the putative $GABA_A$ mediated circuit level mechanism described for propofol, isoflurane and desflurane are also associated with large amplitude slow oscillations, and coherent frontal alpha oscillations at surgical anesthesia levels. Additionally, isoflurane and desflurane are also associated with frontally coherent theta (4–8 Hz) oscillations at surgical anesthesia levels. Ketamine significantly diminished the amplitude of these oscillations and induced a beta oscillatory dynamic. These observations are consistent with our predictions that $GABA_A$ circuit-level mechanisms are dominant during MDDE anesthesia-induced unconsciousness.

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 to identify the cases studied in this manuscript.

Isoflurane: We identified 13 cases with baseline pre-induction EEG recordings that received isoflurane as the sole hypnotic agent for the maintenance of unconsciousness (isoflurane anesthesia cohort). To study the effects of ketamine on isoflurane anesthesia-induced EEG signatures, we also identified 10 age-matched cases where ketamine (mean ± STD: 180 ± 34 mg) was administered for the induction of general anesthesia and isoflurane was administered as the sole hypnotic agent for the maintenance of unconsciousness and (isoflurane/ketamine anesthesia cohort). For data analysis, we chose the first artifact-free consecutive 1 minute EEG segment during the baseline recordings (eyes closed period before the induction of general anesthesia) and during stable isoflurane administration between 15 and 30 minutes after the induction of general anesthesia and airway instrumentation, but before surgical stimulation.

Desflurane: We identified 9 cases that received desflurane as the sole hypnotic agent for maintenance of unconsciousness (desflurane anesthesia cohort). We could not identify in our database desflurane cases with baseline EEG recordings. To study the effects of ketamine on desflurane-induced EEG signatures, we also identified 9 age-matched cases with ketamine (53.3 ± 10 mg, followed by an infusion at 5 μg/kg/min) administered as an analgesic adjunct (desflurane/ketamine anesthesia cohort). For data analysis, we chose the first artifact-free consecutive 1 minute EEG segment during stable desflurane administration occurring at least 15 minutes after the induction of general anesthesia and airway instrumentation. The selected epochs occurred after the onset of surgery.

Frontal EEG data were recorded with the Sedline EEG monitor (Masimo Corporation, Irvine, CA) with a pre-amplifier bandwidth of 0.5–92 Hz, and a sampling rate of 250 Hz. 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. We selected EEG data segments with information from both the electronic anesthesia record (Metavision, Dedham, MA) and EEG analysis in the spectral domain. We visually examined the spectrogram to ensure that the EEG dynamics were approximately stable (i.e., not transitioning to burst suppression or emergence). The electronic medical record was used to identify the sole hypnotic agent administered. None of the patients had known neurological or psychiatric disorders that may have interfered with the EEG. Tables 1 and 2 summarize the patient characteristics and the co-administered medications, respectively.