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Review Article

REVIEW ARTICLE

Human neural correlates of sevoflurane-induced unconsciousness

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Abstract

Sevoflurane, a volatile anaesthetic agent well-tolerated for inhalation induction, provides a useful opportunity to elucidate the processes whereby halogenated ethers disrupt consciousness and cognition. Multiple molecular targets of sevoflurane have been identified, complementing imaging and electrophysiologic markers for the mechanistically obscure progression from wakefulness to unconsciousness. Recent investigations have more precisely detailed scalp EEG activity during this transition, with practical clinical implications. The relative timing of scalp potentials in frontal and parietal EEG signals suggests that sevoflurane might perturb the propagation of neural information between underlying cortical regions. Spatially distributed brain activity during general anaesthesia has been further investigated with positron emission tomography (PET) and resting-state functional magnetic resonance imaging (fMRI). Combined EEG and PET investigations have identified changes in cerebral blood flow and metabolic activity in frontal, parietal, and thalamic regions during sevoflurane-induced loss of consciousness. More recent fMRI investigations have revealed that sevoflurane weakens the signal correlations among brain regions that share functionality and specialization during wakefulness. In particular, two such resting-state networks have shown progressive breakdown in intracortical and thalamocortical connectivity with increasing anaesthetic concentrations: the Default Mode Network (introspection and episodic memory) and the Ventral Attention Network (orienting of attention to salient feature of the external world). These data support the hypotheses that perturbations in temporally correlated activity across brain regions contribute to the transition between states of sevoflurane sedation and general anaesthesia.

Key words: general anaesthesia; anaesthetic mechanisms; electroencephalography; functional neuroimaging

Introduction

Sevoflurane and other volatile anaesthetics are the principal agents used for maintaining clinical general anaesthesia. Additionally, sevoflurane is well-tolerated for inhalation induction, providing a means of elucidating the neural changes associated with gradual transitions from wakefulness through sedation and beyond the loss of consciousness. The mechanistic cascade from molecular interactions to the suppression of consciousness has yet to be fully characterized. Potential downstream functional targets for sevoflurane include brain

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networks associated with attention, cognition, and the maintenance of consciousness. Thus, sevoflurane might serve as a paradigm for understanding mechanisms underlying the therapeutic actions of other halogenated ethers.

Framing the problem of anaesthetic-induced unconsciousness

For over two decades, there has been a systematic search for neural correlates and the underpinnings of conscious experience. One approach to this question relates to information synthesis in the brain, a focus motivated by known phenomenological and neurobiological facts. The known phenomenological fact is that our perception of the world is unified—we do not, for example, experience the colour, shape and warmth of the sun as disconnected elements, but rather as a singular whole. The known neurobiological fact is that the brain is subdivided into discrete functional units that independently process sensory modalities (such as vision) and sub-modalities (such as colour). It is therefore critical that the brain has mechanisms to synthesize discrete neural processing in order to generate the unity of experience. If such synthesis is *necessary* for normal consciousness, it stands to reason that the interruption of this synthesis would be *sufficient* for unconsciousness.

"Connectivity" is a surrogate for integration in the brain and can be assessed from neuroimaging or neurophysiological data. Four types of brain connectivity are commonly analyzed:[1–3] (1) **structural connectivity**, which refers to the synaptic connections between brain regions, (2) **functional connectivity**, evaluated from the covariation of activities within different brain regions over time, (3) **directed connectivity**, determined as a statistical interdependence of neural activities in one area relative to another region in the past, and (4) **effective connectivity**, which uses models to infer a causal relationship between the activities of different brain regions. There are advantages and disadvantages to each of these approaches and the various techniques within each of these categories come with assumptions. In this article, we focus primarily on functional connectivity (e.g. as measured through functional magnetic resonance imaging (fMRI) and directed connectivity (e.g. as measured through EEG).

Models for the effects of general anesthesia on consciousness must accommodate the current framework of how signals in the central nervous system are encoded, transmitted, and decoded across multiple scales of space and time. Neural activity is constrained by the current framework of how information is encoded, transmitted, and decoded in the central nervous system. Neurones at a microscale level temporally integrate inputs and transmit either excitatory or inhibitory output in a binary manner. Both types of neurones serve as building blocks of circuits at a mesoscale level. Circuits distributed across the brain can be localized or distributed across brain structures to provide neural markers at a macroscale level. Models for the integration of neural activity across functionally specialized brain regions incorporate these markers to allow inferences based on the phenotype and behaviour at an organismal level.

Direct and indirect actions on cortical neurones

Sevoflurane binds to protein targets on the surface of neurones, but the precise molecular interactions and the neural structures involved in the induction of unconsciousness have yet to be identified. Electrophysiologic effects correspond to sevoflurane interactions with γ-aminobutyric acid (GABA),[4–7] N-methyl-D-aspartate (NMDA),[8 9] and nicotinic acetylcholine (ACh) receptors;[10] and voltage-gated sodium channels,[11] hyperpolarization-activated cyclic nucleotide-gated (HCN) channels[12] and two-pore domain[13] potassium channels. Whether the relative expression of these proteins on the surface of cortical neurones contributes directly to the unresponsive phenotype remains unknown. *In vivo* studies have supported the roles of GABA-A receptors,[14 15] ACh receptors,[16 17] and HCN channels[18–20] as potential targets for the hypnotic effects of sevoflurane.

Cortical effects of sevoflurane are also likely mediated through arousal centres in the brain. Sevoflurane directly activates adrenergic neurones in the rat locus coeruleus,[21] potentially contributing to clinical agitation during induction and emergence from general anaesthesia. There are no reports regarding the effects of sevoflurane on dopaminergic centres in the ventral tegmental area, the histaminergic nuclei of the tubermammillary nucleus of the hypothalamus, or the cholinergic centre of the nucleus basalis in the basal forebrain. The attenuation of excitatory output from these subcortical structures by sevoflurane would have downstream effects on cortical neuronal excitability that are measureable from the scalp when synchronized across large populations of neurones.

Visually detectable frontal EEG markers

Wave-like patterns in the frontal EEG provide an estimation of intraoperative "anaesthetic depth" during sevoflurane surgical anaesthesia. The oscillatory waveforms can be described by the dominant frequencies in the EEG, with conventionally monitored frequency bands between 0.5 Hz and 30 Hz. The proportion of delta (0.5–4 Hz), theta (4 to 8 Hz), and alpha (8 to 13 Hz) power can vary across states of general anaesthesia, with lower frequencies dominating at greater sevoflurane concentrations. Alignment of alpha waves in bilateral EEG tracings can also be observed (Fig. 1A). Both slow (<1 Hz) and higher frequency (1 Hz to 4 Hz) delta waves are prominent at sevoflurane concentrations typical of general anaesthesia [e.g. approximately 0.9 age-adjusted minimum alveolar concentration (MAC)]. Delta oscillations do not appear to be aligned across interhemispheric frontal EEG signals (Fig. 1B). Concentrations of sevoflurane associated with general anaesthesia can also produce burst suppression, persistent suppression,[22] and epileptiform activity.[23] The sevoflurane concentration at which these phenomena occur may be lower in patients who have increased sensitivity to volatile anaesthetics (e.g. older adults). All these visually recognizable patterns are informative in isolation or for interpreting processed EEG measures.

Frontal EEG power and coherence

Quantitative measurements of oscillatory EEG waveforms provide useful markers for neuromonitoring during sevoflurane general anaesthesia. The strength of rhythmic activity is described by the amplitude or power for a particular frequency range. The power can be computed across time segments and graphed as a compressed spectral array or spectrogram, with delta, theta, and alpha oscillations predominant during sevoflurane anaesthesia (Fig. 1C).[24]

The characteristics of frontal EEG oscillations during the maintenance of sevoflurane general anaesthesia appear to evolve as humans age. The amplitude of the EEG increases as infants age,[25 26] plateaus in early adulthood,[26] and appears to fall off with senescence.[27] The background EEG varies