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Modeling the Dynamical Effects of Anesthesia on Brain Circuits

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Abstract

General anesthesia is a neurophysiological state that consists of unconsciousness, amnesia, analgesia, and immobility along with maintenance of physiological stability. Despite use of general anesthesia in the United States for more than 166 years, how these drugs act in the brain and central nervous system to create this state remains incompletely understood. Propofol is one of the most widely used and the most widely studied anesthetics. When administered for general anesthesia or sedation, the electroencephalogram (EEG) under propofol shows highly structured, rhythmic activity that is strongly associated with changes in the patient’s level of arousal. These highly structured oscillations lend themselves readily to mathematical descriptions using dynamical systems models. We review recent model descriptions of the commonly observed EEG patterns associated with propofol: paradoxical excitation, strong frontal alpha oscillations, anteriorization and burst suppression. Our analysis suggests that propofol’s actions at GABAergic networks in the cortex, thalamus and brainstem induce profound brain dynamics that are one of the likely mechanisms through which this anesthetic induces altered arousal states from sedation to unconsciousness. Because these dynamical effects are readily observed in the EEG, the mathematical descriptions of how propofol’s EEG signatures relate to its mechanisms of action in neural circuits provide anesthesiologists with a neurophysiologically-based approach to monitoring the brain states of patients receiving anesthesia care.

Introduction

General anesthesia is a fascinating man-made, neurophysiological phenomenon that has been developed empirically to enable safe and humane performance of surgical and non-surgical procedures. The state consists of unconsciousness, amnesia, analgesia, and...
immobility along with maintenance of physiological stability. In the United States, more than 60,000 patients receive general anesthesia daily.[1,2] Despite use of general anesthesia in this country for more than 166 years, how these drugs act in the brain and central nervous system to create this state remains incompletely understood. Mathematical modeling has been used in anesthesiology to study the dynamics of anesthetic binding at specific receptor sites, to provide pharmacokinetic and pharmacodynamic descriptions of anesthetic behavior within the body, [3–5] and to describe specific brain states such as burst suppression.[6,7]

There is now growing interest in using modeling studies to describe anesthetic actions in neural circuits.[8–18]

Propofol, 2,6 di-isopropyl-phenol, is one of the most widely used anesthetics. This drug is administered for induction of general anesthesia, maintenance of sedation, and in combination with a narcotic and a muscle relaxant for maintenance of general anesthesia. Propofol acts enhance inhibition at GABA_A receptors, which are widely present throughout the brain and central nervous system.[19] Binding of propofol to the post-synaptic GABA_A receptors on a pyramidal neuron helps maintain chloride channels in the open state, thus enhancing the inward chloride current, which hyperpolarizes the post-synaptic cell and leads to inhibition [19]. The behavioral effects of propofol depend critically on how much and how rapidly the anesthetic is administer, in addition to the physiological state of the patient, i.e. age, weight and co-morbidities [20], and the presence of other arousal potentiating medications.

Propofol’s behavioral effects are strongly associated with highly structured oscillatory patterns in the electroencephalogram (EEG), local field potentials and in neural spiking activity.[21–23]. The highly reproducible nature of these patterns suggest that they relate to the mechanisms through which propofol’s binding at GABA_A receptors leads to strong coordinated network activity throughout major portions of the brain. Because much is known about brain circuit architecture, the highly rhythmic features in these patterns suggests that mathematical modeling research can make important contributions to our understanding of propofol’s actions in neural circuits, and as a consequence, how this anesthetic produces its altered states of arousal.

In this review, we summarize recent work using mathematical models to investigate the dynamical effects of propofol on brain circuits.

1. Paradoxical Excitation

Propofol is well-known to induce paradoxical behavioral and electrophysiological manifestations of excitation, rather than sedation, at low doses [24–27]. A common EEG marker for this paradoxical excitation is elevated power in the Beta (12.5–25Hz) frequency band [25]. Despite these characterizations, the neuronal mechanisms that underlie the low-dose effects of propofol were not well understood.

Recently, a detailed computational model was developed in order to elucidate these mechanisms [9]. The model attributes the generation of Beta-band activity at low doses of propofol to cortical dynamics involving the interaction of pyramidal neurons with two type of inhibitory interneurons. The model specifically focusses on the role of the M-current, a
slow potassium current, in low-threshold spiking (LTS) interneurons [28]. Propofol is modeled as a potentiation of the conductance and time constant of the GABA_A synaptic current [29]. A low dose of propofol is modeled as inducing up to a twofold increase in each of these parameters. At such levels, the interaction between the GABA_A synaptic current and the M-current creates a dynamical transition from synchrony to antisynchrony in networks of cortical interneurons (see Figure 1A, B). At the population level, this antisynchrony manifests as an increase in the spiking frequency of pyramidal neurons into the Beta range. By modeling the collective activity of these pyramidal neurons as a surrogate for the EEG [30], the model thus predicts paradoxical excitation as a collective state of cortical interneuron antisynchrony mediated principally by LTS cells. A detailed mathematical analysis of this model was subsequently performed in [31]. There, in a highly reduced version of [9], the authors used geometric singular perturbation theory to show how the M-current and GABA_A interplay is highly specific to the low dose regime. The essential dynamical mechanism in this regime was revealed to be the creation of post-inhibitory rebound spiking in LTS interneurons.

Other modeling efforts on propofol have used a mean-field models that describe neuronal dynamics at the scale of cortical macrocolumns [32,33]. These approaches focus on electrophysiological phenomena at deeper levels of general anesthesia. They do not include mechanisms of spike-frequency adaptation, such as those created by the M-current, that may be essential in low-dose paradoxical excitation [34]. A recent exception is [35], in which a linear mean-field model was developed that exhibits increases in frequency at certain levels of GABA_A inhibition due to an oscillatory instability in the model dynamics.

2. Thalamocortical Networks and Alpha Oscillations

At deeper levels of propofol, the paradoxical effects described above give way to the more well-known behavioral endpoints of sedation and, eventually, unconsciousness [1]. Classically, these states have been associated with the manifestation of low-frequency delta (1–4 Hz) activity in the EEG [25,26]. Recent evidence, however, suggests that the point at which propofol induces unconsciousness is well-characterized by the appearance of a highly coherent alpha (9–13 Hz) rhythm in frontal cortices [21–23].

Building on the work of [9], a model was developed to explain the genesis of this alpha rhythm [10]. The model explicitly takes into account the thalamus, a structure that is well known to mediate oscillatory activity in the alpha range during sleep [36]. Several models have been developed to describe these thalamic dynamics, centered on the so-called spindle oscillation [37–39]. The model in [10] includes both thalamic and cortical components. A high dose of propofol is modeled as a 300–400% increase in GABA_A conductance and time-constant. It is shown that at such levels, the cortical dynamics exit the paradoxical Beta regime of [9] and enter an alpha frequency regime mediated by the time-constant of inhibition. Meanwhile, the increased levels of GABA_A in the thalamus lead to enhanced post-inhibitory rebound spiking mediated by the hyperpolarization activated current (h-current). This enhancement strengthens the already present alpha mechanisms of [37–39]. The reciprocal coupling between thalamus and cortex serves to reinforce this oscillation, leading to prolonged periods of alpha activity (see Figure 1A, C). The model further shows...
that this activity synchronizes between cortical regions via the thalamus, leading to high spatial coherence. Figure 2A, C demonstrates the Beta and Alpha phenomenology described above in an EEG recording of a human subject receiving an increasing dose of propofol (from [18]). This phenomenology is well-matched by the model output in Figure 2B, D.

Other thalamocortical models of neural activity during general anesthesia include [14], which focused primarily on delta and theta frequencies. Very detailed models of the thalamocortical system have also been developed to study the transition from awake to natural sleep [13]. Mean-field type models of propofol anesthesia, as discussed above, generally do not include the thalamus, focusing instead on cortical dynamics. The general focus of these models has been on explaining the origin of slower frequency delta oscillations [11,15–17,40,41], due to a range of anesthetic drug effects beyond GABA-ergic increase. In the absence of full thalamocortical interactions, however, the alpha-rhythm regime for propofol may be difficult to completely model [16,18].

3. Anteriorization

The alpha oscillations described above at deep levels of propofol have a distinct spatial structure. Namely, these oscillations manifest predominantly in frontal regions [21,23,42]. This lies in contrast to the classical occipital alpha rhythm associated with eye closure during wakefulness [36,43]. Indeed, while the frontal alpha emerges at propofol-induced unconsciousness, the posterior occipital alpha is attenuated [21,23,44]. Collectively, the gain in anterior power, concurrently with loss in posterior power, has been described as a phenomenon of anteriorization [1,23,45].

A recent model has been developed that describes neuronal mechanisms that may underlie this anteriorization of alpha rhythms [46]. The model combines thalamocortical mechanisms in frontal [10] and posterior [47] projecting thalamic nuclei. The primary mechanism involves propofol-mediated reduction in the conductance of the hyperpolarization activated current (h-current) [48,49], in addition to its GABAergic effects. The h-current attenuation alters the dynamics of the high-threshold thalamocortical neurons thought to mediate the generation of the occipital alpha [47], leading to an overall attenuation in posterior alpha rhythms. Meanwhile, the reduction in h-current does not significantly affect the GABA-mediated alpha genesis in frontal thalamocortical circuits [10,46]. Consequently, anteriorization can be understood as a combined effect of propofol on GABA and the h-current, with specific effects on different thalamic nuclei based on cell-type (see Figure 3A).

4. Burst Suppression

At deeper still levels of propofol, the EEG exhibits the phenomenon of burst suppression, in which high amplitude activity alternates with periods of isoelectric quiescence [1]. It is a transitional state that occurs between the levels of propofol described above and a state of complete EEG flatline. The amount of suppression increases as a function of anesthetic depth this flatline is achieved. The electrophysiological properties of burst suppression include a broad spatial expression across the cortex and quasiperiodicity in the onset and offset of bursts [50,51].
Efforts to model burst suppression have been limited, due to an inability to account for the many etiologies in which the phenomenon arises. These include propofol anesthesia, but also pathological states such as hypothermia [52], hypoxic/ischemic coma [53], and certain infantile encephalopathies [54]. To account for this diversity of etiologies, a recent model has described burst suppression as arising from an interaction of neuronal and metabolic dynamics [6]. The model postulates that each of the conditions associated with burst suppression is linked by a significant reduction in cerebral metabolic rate [55]. To describe this, the model introduces an ATP sensitive potassium channel into all neurons. When ATP levels decrease below a critical threshold, these channels open, causing neurons to cease production of action potentials [56]. In the model, the reduction in cerebral metabolic rate is introduced via a parameter that governs the rate of ATP regeneration. The Sodium-ATP pump is the primary consumer of ATP via production of action potentials. In a normal metabolic regime, the regeneration of ATP is sufficient to sustain action potential production at rates dictates by the natural dynamics of the circuit in question. When ATP production is depressed, however, the ATP sensitive potassium channel is activated due to insufficient supply and spiking activity stops until such time as sufficient ATP levels are restored. In this sense, the model describes the periods of suppression as transient phases of metabolic recovery when the overall energetic state of the brain is depressed (see Figure 3B, C). Many of the predictions garnered from this model have recently been verified in human intracranial recordings [57], which additionally provides a more detailed spatial characterization of burst and suppression dynamics.

The phenomenon of burst suppression has also recently been modeled at a mean-field theory representations.[7] This model extends the mean field descriptions of brain dynamics under anesthesia [12,58] by introducing more abstract slow variables associated with synaptic resource depletion during sustained periods of population activity. The rate of depletion is related to the level of anesthesia. While a biophysical mechanism for this rate modulation is not explicitly given, it is suggested that, as in [6], this could be related to reductions in cerebral metabolism. The dimensionality of the field modeling approach in [7] makes tractable dynamical analyses over larger scale that are harder for the detailed biophysical approach, at the loss of specific mechanistic explanatory capability. A combination of modeling approaches is likely to prove most effective for describing completely the dynamics of propofol and other anesthetics.

5. Conclusion and Future Directions

The altered states of arousal induced by propofol are strongly coupled to highly structured EEG oscillations. Mathematical modeling can be used to gain insight into the mechanisms of these oscillations, and as a consequence, the mechanisms through which propofol induces its altered arousal states. Administering propofol for general anesthesia or sedation is equivalent to applying simultaneously strong inhibitory inputs to the brainstem, thalamus and cortex. However, because the brain is a high-dimensional dynamical system, with myriads of interconnections and feedback loops, this inhibition does not turn the brain off, but rather, induces highly structured oscillatory dynamics. Most of these oscillations are several times larger than the oscillations observed in the resting EEG of an eyes open subject. The profound nature of the oscillations burst suppression supports the idea that
Propofol entrains large numbers of brain circuits to act in a coordinated manner. These coordinated dynamics are likely responsible for propofol’s altered states of arousal.

Further modeling work with propofol tightly coupled with experimental studies and analyses will lead to deeper insights into the characteristics of its effects on brain dynamics. For example, anteriorization and strong frontal alpha oscillations show that there are different dynamics between the anterior and posterior parts of the brain during propofol-induced unconsciousness. The timing of this difference in dynamics is consistent with the timing of loss of fronto-parietal functional connectivity that has been identified marker of propofol-induced unconsciousness. Hence, the mechanisms underlying anteriorization and the strong frontal alpha oscillations likely also contribute to loss of fronto-parietal connectivity [59–61].

Combined modeling and experimental research applied to other anesthetics, such as ketamine and dexmedetomidine would also be beneficial. Ketamine and dexmedetomidine act in the same circuits as propofol yet, they target primarily NMDA and alpha 2 adrenergic receptors respectively. Both anesthetics have profound effects on brain dynamics and produce anesthetic states that differ appreciably from those induced by propofol. [1,23,62]

In general, using mathematical models to help understand how the EEG signatures of anesthetics relate to their mechanisms of action in neural circuits is important scientifically and also practically as it provides anesthesiologists with an interpretable, neurophysiologically-based approach to monitoring the brain states of patients receiving anesthesia care.

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Key Points

- Propofol acts on GABAergic circuits in the cortex, thalamus and brainstem.
- Propofol-induced oscillations in these circuits induce changes in arousal level.
- Alpha and slow oscillations are markers of propofol-induced unconsciousness.
- Burst suppression is likely due to cyclic depletion of the brain’s energy stores.
Figure 1.
Thalamic and cortical dynamics for low- and surgical-dose levels. (A) In a baseline regime, the thalamocortical system functions through interactions between four principle cell types: Cortical pyramidal neurons (PY), Interneurons (LTS/FS), Thalamic Reticular Neurons (RE) and Thalamocortical neurons (TC). (B) At low doses of propofol, a moderate increase in GABA_A interacts with the hyperpolarization-activated current I_h in interneurons to create a primarily cortical Beta oscillation [9]. (C) At higher (surgical) dose levels, the effects on GABA_A increase in both cortical and thalamic networks, creating alpha (10–13Hz) time-scales paced by the decay-rate of the inhibition [10]. The reverberant connections between thalamic and cortex reinforces this oscillation, leading to broad and coherent alpha expression in the EEG. Figure adapted from [10].
Figure 2.
EEG phenomena in the transition from baseline to surgical levels of propofol. (A) Spectrogram of human EEG showing the emergence, sequentially, of diffuse Beta- and narrow Alpha-band oscillations. (B) The output of the thalamocortical model matches this phenomenology. The same is true when comparing the EEG coherence between the actual data (C) and model (D). Figure adapted from [10].
Figure 3. Secondary effects of propofol lead to anteriorization and burst suppression. (A) The differential structure and cell types (in particular, high-threshold thalamocortical neurons) of fronto-thalamic versus posterior-thalamic networks leads to the phenomenon of Anteriorization [23,46,47]. (B) At very high doses, propofol leads to secondary effects on cerebral metabolism which can be modeled as a disruption to the rate of ATP regeneration in local circuits. (C) This disruption causes periodic cessation of neuronal activity when ATP levels drop below threshold-levels. This cessation, in turn, manifests as the phenomenon of EEG burst suppression [6]. Figure adapted from [6,46].