

Anesthetic Suppression of Thalamic High-Frequency Oscillations: Evidence that the Thalamus Is More Than Just a Gateway to Consciousness?

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WHAT DOES ANESTHESIA DO TO THE BRAIN?

Despite over a century of investigation, we still lack a full answer to this fundamental question.¹ We know many of the molecular targets on which anesthetics act, but we do not fully understand how these molecular effects give rise to circuit-level or region-specific changes in brain activity. Furthermore, we know virtually nothing about how or why small changes in anesthetic concentration during a case can alter the incidence of delirium and postoperative cognitive dysfunction days² to months³ later.

Our lack of understanding of how anesthetics affect the brain and long-term cognitive outcomes is not surprising, though, considering the vast complexity of the human brain, which contains approximately 86 billion⁴ neurons with an estimated 125 trillion connections. However, the neurophysiologic changes that accompany the descent from consciousness into general anesthesia may provide a “toehold” for understanding how the complex structure of the brain processes information. In this sense, anesthesia is a natural tool to understand how cellular and circuit-level phenomena give rise to behavior before deciphering more complex executive functions or emotions. Furthermore, given the upcoming American Society of Anesthesiologists Brain Health Initiative, it is timely and important for anesthesiologists to develop a mechanistic understanding of how anesthetic drugs affect the brain. Realizing this goal can help us to achieve the clinical endpoints of general anesthesia and to ensure optimum postoperative cognitive function for our patients.

In this issue of *Anesthesia & Analgesia*, Plourde et al.⁵ contribute to our understanding of how anesthetic drugs affect the brain. Specifically, the authors examine how isoflurane modulates neural activity patterns in two important brain regions for information processing, the cerebral cortex and the thalamus. Because these two regions are critically important for cognition and attention, neuroscientific research has intensely focused on their association with each other. A brief reflection on these brain regions helps us to understand these results in the proper scientific context.

The cerebral cortex has mountain-like gyri separated by intervening valleys (known as sulci) that gives the outer surface of the human brain its classic “wrinkled” appearance. The cerebral cortex is thought to process the neuronal information that gives rise to complex human thought and behavior (e.g., planning, thinking). The thalamus lies deeper within the brain (Fig. 1) and has afferent and efferent connections with both cortical and subcortical areas. The thalamus is often referred to as a “gate” because it controls ascending information from subcortical arousal centers (such as the tuberomammillary nucleus, pontine reticular formation, and locus coeruleus) to the cortex.

By emphasizing the gate metaphor, however, it is tempting to overlook the importance of the thalamus as nothing more than a threshold-activated “switch” for cortical activation. For example, in sleep, the cortex is less responsive

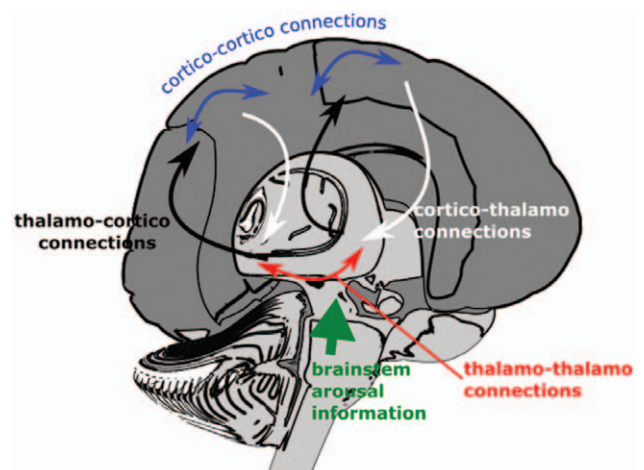


Figure 1. Neural connections among the thalamus, cortex, and brainstem.

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to mild stimulation (i.e., whispering), but if enough environmental stimulation is presented (i.e., an alarm clock), the information can open the thalamic gate, reach the cortex, and awaken us. However, just as crossing Berlin's *Brandenburg Gate* represented a fundamental transformation from the Iron Curtain to Western freedom at the end of the cold war, the thalamus represents more than a simple passageway for sensory information: it represents a point of information transformation. Environmental sensory input stops in the thalamus for processing before being sent to the cortex, and information from one cortical region is also modified in the thalamus before further processing in other cortical regions. In addition to input from the brainstem, connections exist among the thalamic nuclei (thalamo-thalamo connections), from thalamus to cortex (thalamocortical connections), and from cortex to the thalamus (corticothalamic connections). The presence of these prominent corticothalamic connections suggests that the thalamus is an important player in transforming information from the cortex^{6,7} rather than simply relaying information to the cortex.

Thalamic lesions typically lead to a global loss of consciousness.⁸ Conversely, thalamic excitation can produce an aroused/awake state even amid isoflurane doses that would normally produce unconsciousness^{9,10} and was sufficient to increase consciousness in a patient with severe traumatic brain injury.¹¹ During isoflurane-induced unconsciousness, thalamic and cortical firing in vivo becomes synchronized.¹² Like slow-wave sleep, profound depressions in consciousness are associated with a change in the firing pattern of thalamic neurons from irregular but consistently active ("tonic firing") to more rhythmic "bursting" patterns (reviewed in reference 13). These synchronous neuronal firings can be detected by local field potentials and cranial electroencephalogram (EEG) in rodent models and by EEG recordings in humans.

During waking behaviors, thalamocortical neuronal activity (in the frontotemporal cortices) is typified by moderate-amplitude voltage oscillations in the gamma frequency range (approximately 40–80 Hz) (reviewed in reference 14). Thalamocortical gamma frequency oscillations are essential for conscious perception and cognitive tasks¹⁵ and are thought to be a neural correlate of conscious perception.¹⁶ These gamma frequency oscillations are also the first EEG frequency band to change during transitions in and out of consciousness.^{17,18} With the notable exception of ketamine,¹⁹ general anesthesia is typically accompanied by a suppression of gamma EEG frequencies and a transition to higher amplitude, slower frequencies (8–14 Hz).^{17,18,20} Less is known about the high gamma oscillations (80–200 Hz), which are sometimes referred to as ripples.²¹

WHAT DOES THIS PAPER SHOW?

Reed and Plourde²² confirm that like propofol, isoflurane attenuates thalamic gamma frequency oscillations (30–200 Hz) in a concentration-dependent manner.⁵ They also demonstrate that isoflurane attenuates these gamma frequency oscillations in the cortex to a greater extent than does propofol.²² The authors used concentrations of isoflurane and propofol that were equipotent at producing loss of the righting reflex, but they note that their results may have

differed if they used alternative behavioral endpoints that require higher anesthetic doses (e.g., suppressing reaction to noxious stimulation). Perhaps most importantly, for both propofol and isoflurane, the suppression of high gamma frequency oscillations was more pronounced in the thalamus than that in the cerebral cortex. This provides strong support for the notion that unconsciousness is associated with impairment of thalamic activity and suggests that corticothalamic activity is necessary for consciousness.

WHAT DO THESE FINDINGS MEAN?

Traditionally, the cerebral cortex is considered to be the part of the brain that makes us human, and the integration of cortical information has been suggested as an explanation of our normal conscious states. The thalamic field potential recording data presented by Plourde et al.^{5,22} force us to reconsider this view. Local field potential recordings mainly represent postsynaptic dendritic depolarizations rather than axonal action potentials. Because the high-frequency input to the thalamus is the frequency bandwidth most affected at anesthetic-induced unconsciousness, this suggests that these high-frequency corticothalamic inputs are important for producing/maintaining consciousness. In the context of current theories on the "binding" of consciousness,²³ these results suggest that thalamic processing of corticothalamic information plays an equally important role in producing consciousness as the cortical processing of thalamocortical information. It is possible that cortical integration of information that translates into a conscious phenomenon must involve "closing the information loop" via a cortico-thalamocortical network.

In addition to providing insight into mechanisms of consciousness, these results clarify the neurophysiologic mechanisms that underlie the pharmacodynamic effects of different anesthetic agents. For example, the steeper dose-response curve for isoflurane versus propofol for cortical gamma frequency power suppression is notable⁵ and could even explain several clinical differences between these drugs. First, this finding could explain why a higher awareness rate has been found after cases in which anesthesia is maintained with propofol (i.e., total IV anesthesia) versus inhaled agents,²⁴ although clearly this could also be explained by the lack of an effect-site proxy monitor for propofol (e.g., an equivalent of end-tidal monitoring for propofol). Second, perhaps the steeper dose-response curve for cortical gamma suppression by isoflurane than propofol may explain why propofol has been associated with a higher rate of intraoperative dreaming than inhaled agents in some^{25,26} (although not all²⁷) studies. Perhaps, isoflurane abolishes the cortical activity that mediates dreaming (i.e., gamma frequency power) to a greater extent than propofol.

WHERE DO WE GO FROM HERE?

The findings of Plourde et al.⁵ and Reed and Plourde²² bring us one step closer in our epic quest to understand how anesthetics affect the brain. A full answer to this question¹ will require multiple levels of analysis, from an understanding of how the molecular effects of anesthetics give rise to alterations in cellular and synaptic function, which then change circuit and brain region level activity patterns to ultimately produce the cognitive and behavioral picture that we intuitively recognize as general anesthesia. This is a massive

project. However, there should be no doubt that this work is essential for us to better understand what our drugs are doing to our patients' brains and how to promote healthy neurocognitive function for our patients afterward. Our patients deserve no less. ■■

DISCLOSURES

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