Consciousness, Anesthesia, and the Thalamocortical System

ETYMOLOGICALLY, "thalamus" derives from the Greek *thalamos*, meaning "inner chamber," and *tholos*, meaning "vault."[1] Neurobiologically, the thalamus is a bilateral structure in the diencephalon comprising approximately 50 nuclei and subnuclei with rich interconnections to other structures in the brain. Thalamic nuclei can be classified as specific (mediating relay of peripheral information to a particular area of sensory cortex) and nonspecific (mediating multimodal integration of information). In this issue of ANESTHESIOLOGY, Liu *et al.*[2] unlock the vault of the thalamus by using magnetic resonance imaging to differentiate the role of specific and nonspecific thalamocortical systems in propofol-induced unconsciousness.

To appreciate the findings of Liu *et al.*, it will be helpful to consider four potential roles of the thalamus in the mechanism of general anesthesia.

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1. Thalamus as a "switch" of anesthetic-induced unconsciousness

In this framework, the thalamus serves as an On–Off switch for consciousness. The thalamic switch hypothesis[3] was based on human neuroimaging studies identifying thalamic depression as a common feature of both inhaled[4,5] and intravenous[6] anesthesia. This Off-switch model focused on the hyperpolarization of the thalamus, leading to a shift from tonic to burst firing that—as with sleep—blocks sensory information from arousing the cortex and maintains subjects in an unconscious state. Further work has supported the depression of the thalamus as a common feature of anesthetic-induced unconsciousness across multiple drug classes.

Subsequent studies in animal models demonstrated that the thalamus could also function as an "On" switch that reverses anesthesia. Infusion of nicotine[7] or antibodies blocking a voltage-gated potassium channel[8] into the centromedial thalamus was shown to reverse the effects of inhaled anesthetics in rats, leading to a restoration of consciousness. This finding was consistent with studies in humans with traumatic brain injury, in which central thalamic stimulation was associated with behavioral improvements.[9]

2. Thalamus as a "read-out" of anesthetic-induced unconsciousness

Neuroimaging with magnetic resonance or positron-emission tomography is associated with good spatial resolution but poor temporal resolution, leaving us to wonder whether the thalamus is leading or following the parade of anesthetic-induced unconsciousness. In 2007, Velly *et al.*[10] published a neurophysiologic study of humans implanted with deep brain stimulators for Parkinson disease. The investigators performed electrophysiologic recording from electrodes on the scalp (reflecting cortical potentials) and in the subthalamic nuclei (reflecting subcortical potentials) while patients underwent general anesthesia with either propofol or sevoflurane. Although the deep brain stimulating electrodes were positioned in the subthalamic nuclei, the authors invoked a number of arguments to support the hypothesis that the observed electrical activity originated in the thalamus. Velly *et al.* found that scalp electroencephalography better distinguished consciousness *versus* unconsciousness compared with subcortical signals and therefore argued that, based on a method with superior temporal resolution, the cortex was the site mediating anesthetic-induced unconsciousness. A subsequent depression of the thalamus might therefore reflect a read-out of diminished cortical activity. This idea is consistent with

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descriptions of consciousness in which the thalamus serves as the "blackboard" on which cortical computations are "written" and integrated.[11,12] A recent neuroimaging study found that propofol-induced unresponsiveness was more closely associated with functional disconnections from the putamen (a subcortical structure in the basal ganglia) rather than the thalamus,[13] again questioning the causal role of the thalamus in anesthetic mechanisms.

3. Thalamus as a "participant" in anesthetic-induced unconsciousness

Yet another possibility is that thalamic or thalamocortical activity participates in perceptual failure during general anesthesia. Using human electroencephalographic data and mathematical modeling, Ching *et al.*[14] proposed that the action of propofol on γ-aminobutyric acid receptor conductance facilitates involvement of the thalamus in synchronous alpha rhythms (10–13 Hz) with the frontal cortex. This synchrony was posited to impair the ability of the thalamus to "project exogenous input." Another investigation proposed hypersynchrony of α as a mechanism of propofol-induced unconsciousness, with the alternative interpretation that flexible corticocortical communication is interrupted as a result of stereotyped oscillations.[15]

4. Thalamus as "epiphenomenal" to anesthetic-induced unconsciousness

How much does the thalamus contribute to consciousness? Earlier studies in cats with a surgically removed thalamus[16] and more recent studies in rats without a thalamus[17] suggest that thalamic activity may not be critical for maintaining a level of consciousness, as athalamic animals do not seem to be unconscious and can even ambulate. However, these animals seem oblivious to their surroundings, leading to the question of whether they simply have brain arousal in the absence of sensory awareness.

The first three roles are not mutually exclusive. For example, relay of information through specific sensory nuclei could be inhibited by general anesthetics (thalamus as switch), whereas diminished cortical computation could reduce input to nonspecific integrative nuclei (thalamus as read-out). The work of Liu *et al.* refines our understanding by focusing attention on the nonspecific thalamus. The investigators employed magnetic resonance imaging to study the effects of propofol on eight subjects in a state of "deep sedation." After the acquisition of the images, during which an auditory verbal memory task was performed, specific and nonspecific nuclei of the thalamus were identified and "seeded" to perform connectivity analysis with regions of the cortex. In aggregate, deep sedation was associated with a reduction of functional connections between the thalamus and the cortex. However, the connections of the specific nuclei—mediating sensory transfer from the periphery—were relatively well preserved. In contrast, the connections of the nonspecific nuclei—mediating integration of cortical computations—were significantly suppressed. These changes were reversed upon recovery of consciousness and, in fact, connections were increased compared with the baseline state. Of note, thalamocortical connections in the left hemisphere were preferentially reduced by propofol compared with the right. Finally, the investigators analyzed the association between the cognitive changes across states and specific *versus* nonspecific nuclei, finding that the activity of the nonspecific nuclei had the strongest correlation with cognitive function.

The study of Liu *et al.* involved only one anesthetic drug and a relatively small sample size but still advances the field by demonstrating that the role of the thalamus in propofol-induced unconsciousness relates primarily to the functional connections of nonspecific nuclei to the cortex. The four potential roles of the thalamus can be reconsidered in light of their findings:

1. **Switch:** The study suggests that the thalamic switch function during anesthesia does not relate primarily to sensory relay.
2. **Read-out:** The study design could not address whether targeted suppression of nonspecific thalamic nuclei is the cause (*i.e.*, the active blackboard for integrating cortical computation is no longer available) or effect (*i.e.,* corticocortical communication and computation is suppressed, obviating the need to connect to the blackboard) of anesthetic-induced unconsciousness.
3. **Participant:** Thalamocortical synchrony may not contribute to anesthetic-induced unconsciousness by a suppression of information transfer from the periphery to the sensory cortex. This interpretation is supported by other recent studies of thalamocortical connectivity and propofol anesthesia.[18]
4. **Epiphenomenon:** Given what appears to be preferential involvement of the nonspecific thalamic nuclei in the cognitive alterations observed by Liu *et al.*, it is unlikely that changes in thalamic activity are simply epiphenomenal to anesthetic mechanisms.

In conclusion, the current study by Liu *et al.* helps us focus future investigation on the role of the nonspecific thalamic nuclei in anesthetic mechanisms by providing details of the inner chamber that may house the secrets of consciousness and anesthesia.

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Hayes Generator No. 3 Finds a Home for the Holidays

In December of 2006, Dr. Selma Calmes (*left*) sent what she called a "Christmas present" to the Wood Library-Museum of Anesthesiology. Her gift was a holiday-wrapped "mystery inhaler" (*right*) that she had purchased from a vendor in southern California. After Museum Registrar Judith Robins unwrapped this item, it was curatorially identified as a Hayes Anaesthetic Apparatus No. 3, the final and most sophisticated "Generator" designed by 1895 by Dr. Samuel J. Hayes of Pittsburgh. (Copyright © the American Society of Anesthesiologists, Inc.)

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