

All Together Now

THE mechanism by which anesthetics impair consciousness remains one of the most important unsolved mysteries of our specialty—if not of all science. Establishing causal links connecting molecular sites of action with cellular, network, and ultimately behavioral changes will be a formidable challenge. One important approach that can contribute to this effort is the use of mathematical models that can synthesize detailed information about individual channels, cellular properties, and interconnections to yield predictions about the behaviors of complex systems. Experiments can be conducted *in silico* to investigate how individual components contribute to network properties in a way that is difficult or impossible using *in vitro* or *in vivo* approaches. In this issue of ANESTHESIOLOGY, Gottschalk and Miotke¹ make use of this computational approach to investigate how anesthetic modulation of two potentially important molecular targets, γ -aminobutyric acid type A (GABA_A) receptors and T-type calcium channels, might contribute to changes in thalamocortical network properties during anesthesia, with the ultimate goal of explaining how anesthetics render us unconscious.

The target of their investigation is a network of inhibitory cells that comprise the reticular nucleus of the thalamus (RTN). The thalamus has long been recognized as the gateway to the cortex, with sensory information transmitted *via* relay cells, the primary projection neurons of the thalamus, to arrive at primary sensory cortex. More recently, the thalamus has also been recognized to play an important, perhaps even dominant, role in the communication between different regions of the cortex *via* indirect corticothalamocortical pathways.² The cells of the RTN provide an inhibitory input to the relay cells, so they are in an ideal position to control the flow of information to and through the cortex.³

A remarkable feature of the activity of both RTN and thalamic relay cells is the presence of two distinct firing modes. During alert wakefulness, these neurons are steadily depolarized and respond to excitatory inputs with streams of unitary action potentials, allowing them to relatively faithfully transmit incoming signals in a relatively linear manner.² However, during certain network states, such as nonrapid eye movement sleep and anesthesia, they synchronize their own firing and that of

their thalamic targets to produce prominent network oscillations that can be observed in the electroencephalogram as sleep spindles, transient bouts of activity that have a dominant frequency of approximately 10 Hz and that occur typically just after the up-state transition during slow wave oscillations of sleep and anesthesia.⁴ Two important characteristics that endow them with this ability are (1) γ -aminobutyric acid-mediated inhibitory synaptic connections that RTN cells make with each other and (2) the presence of low-threshold “transient” T-type Ca²⁺ channels, which produce a slow calcium spike on which bursts of action potentials ride. The well-recognized transition of electroencephalographic activity during anesthesia from low-amplitude desynchronized activity in the awake state to increasingly synchronous large-amplitude oscillations that mimic those occurring during natural sleep (and in fact may well use many of the same elements) provided the motivation for examining the contributions of anesthetic modulation of GABA_A receptors and T-type Ca²⁺ channels to synchronous activity.

The model on which the current study is based was developed using detailed morphologic and electrophysiologic studies of these specific cells and their synapses.⁵ It has been used successfully in the past to model spindle generation by the RTN⁶ and to demonstrate the role of neuromodulators in switching between firing modes.⁷ As demonstrated previously, the model produces a spindle-like rhythm even in the absence of simulated anesthetic effects, though the output is far from synchronous. At first glance, this drug-free characteristic of spindle-like activity seems at odds with a model that is meant to simulate the transition from consciousness to unconsciousness, which is more commonly associated with a transition from tonic to burst firing mode. However, in the quiet resting state, thalamic neurons can respond with bursts to sensory input,⁸ and similarities have been noted between sleep spindles and the α rhythm, a prominent oscillation seen in the electroencephalogram during quiet wakefulness and that may be produced by a similar mechanism.^{9,10} Therefore, although the model as implemented here does not reproduce the stereotypical transition from tonic to burst firing mode associated with the transition from awake to unconscious, it may nevertheless provide an approximation of quiet waking network activity.

An important outstanding question that is particularly applicable to inhaled anesthetics (which can influence essentially any given physiologic process provided that a high enough concentration is administered) is to identify relevant molecular targets and to determine how the typically small effects that are seen at low “sedating” concentrations combine to produce the net effects of

This Editorial View accompanies the following article: Gottschalk A, Miotke SA: Volatile anesthetic action in a computational model of the thalamic reticular nucleus. ANESTHESIOLOGY 2009; 110:996-1010.

Accepted for publication January 7, 2009. Supported by grant Nos. NS56411 and GM47818 from the National Institutes of Health, Bethesda, Maryland. The author is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

these agents. The current study begins to address this question by simulating the effects of halothane and isoflurane on GABA_A receptors and T-type Ca²⁺ channels, using previous reports of their effects in a variety of other systems as surrogates for effects on these specific synapses and channels. Both anesthetics increased network synchrony, thus mimicking qualitatively one of the fundamental characteristics of the electroencephalogram during anesthesia. Unfortunately, there are not yet any physiologic studies of the isolated bursting RTN network to which these findings may be compared directly. (In this regard, this modeling study may serve as a wake-up call to physiologists interested in this question, for it should provide a useful framework for interpreting detailed pharmacologic studies.) Nevertheless, an important outcome of the study is the demonstration that even the modest effects produced by anesthetic concentrations associated with unconsciousness—less than a 20% increase in the decay time constant of GABA_A receptors and a 5% reduction in T-type Ca²⁺ channel currents—combine to produce substantial changes in network synchrony. Although the authors emphasize the similarity in coherence that is produced in the model by these two anesthetics at behaviorally comparable concentrations, it is difficult from these results alone to know whether this reflects a meaningful causal relation among channel modulation, network coherence, and behavioral state or whether it is simply a fortuitous coincidence.

It is interesting that similar changes in coherence can be produced by modulating either GABA_A receptors or T-type Ca²⁺ channels in the model and that the two anesthetics can arrive at a similar point by way of different paths. Using the ability to selectively manipulate each target that the computational approach provides, Gottschalk and Miotke go on to test whether the substantial changes in synchrony that derive from these small anesthetic effects reflect “additive” or “synergistic” effects at the network level, and to more generally explore the effects of combined influences on two separate anesthetic targets using isobolographic analysis. This is a timely topic, as demonstrated by a recent series of experimental and theoretical articles exploring additivity, synergy, and their implications for anesthetic mechanisms.^{11–14} Despite the common expectation that drugs acting at different sites will show synergy, a general rule that was borne out by studies of the interactions among many drug classes of intravenous and inhaled drugs used in anesthetic practice,¹⁴ they found that the combined effects in the model were largely additive. Indeed, deviations from additivity were not only modest but could be either synergistic or antagonistic depending on the specific drug and simulated concentration. This finding fits well with a separate theoretical analysis demonstrating that additivity is expected when drug effects are pro-

duced by concentrations associated with low receptor occupancy.¹³

As do all studies, the current one has clear limitations, as readily acknowledged by the authors (and not surprising given the relative simplicity of the model that was studied) and raises additional questions. If reduced T-type Ca²⁺ channel activity enhances synchrony, and this change is instrumental in altering consciousness as proposed, why do other drugs that block T-type Ca²⁺ channels, such as ethosuximide, not produce hypnosis or sedation? Perhaps anesthetic-induced changes in this specific rhythm contribute to other aspects of thalamocortical function, such as sensory gating, as demonstrated recently for control of visceral pain sensation.¹⁵ Clearly the activity of the thalamus is dramatically altered by anesthetics, but is the thalamus itself a critical target of these drugs? Or does its change in activity reflect altered inputs from below, above, or both? Given the accumulating evidence that the state of “anesthesia” shares many essential mechanisms with natural sleep¹⁶ and the well-established role of the thalamus in sleep and consciousness, further studies of anesthetic modulation of thalamic function that can clarify its role in producing this essential component of anesthesia are clearly warranted. Few fields of study are as fascinating (or as difficult) as unraveling the mysteries of the mind. But, the powerful combination of physiologic experimentation and computation provides a promising path forward. The authors are to be commended for bringing the sophisticated tools of computation, an essential approach in contemporary neuroscience, to bear on this question.

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■ ANESTHESIOLOGY REFLECTIONS

Cleyer Introduces Europeans to Acupuncture



Published in Frankfurt in 1682 by Johann Zubrodt, this is the first and only edition of Andreas Cleyer's *Specimen Medicinae Sinicae*. Housed in the WLM's K. Garth Huston, Sr. Rare Book Room, Cleyer's classic was actually the first illustrated text on Chinese medicine to be published in the West. *Specimen Medicinae Sinicae* familiarized European readers with Chinese medical philosophies and practices such as pulse diagnosis, meridian theories, and acupuncture therapy. Cleyer's text is "bound in contemporary vellum over boards" with a text published earlier in Frankfurt, J. Clauberg's 1681 *Dictata physica private id est Physica contracta . . .* (Copyright © the American Society of Anesthesiologists, Inc. This image appears in color in the Anesthesiology Reflections online collection available at www.anesthesiology.org.)

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