

What Would a Proper Explanation of Anesthesia Look Like?

Jamie Sleight, M.D., Darren Hight, B.Sc.

OVER the past decade, there has been a proliferation of theories about consciousness and anesthesia. The article by Meyer¹ in this issue of *ANESTHESIOLOGY* reviews some plausible arguments as to how anesthetic drugs might induce unconsciousness. If we want to understand anesthesia, we first need to know *what* the drugs are doing to the central nervous system, and then, second, exactly *how* the effects of these drug are altering the central nervous system function so as to cause the observed behavioral effects of general anesthesia, namely the loss of somatic, autonomic, and cognitive responsiveness to noxious stimuli. It is probably useful to separate the *what* and *how* questions. Currently, we have numerous studies that contribute information regarding the *what* questions, but many fewer answers to the *how* questions. Any complete explanation of anesthesia must include detailed descriptions of *what* processes are occurring at all spatial scales and then also *how* these processes are linked between scales. How does the anesthetic drug bind to the receptors? How does the receptor dysfunction change neuronal activity? How does the altered neuronal activity affect the activity of populations of neurons? How does disturbance in neuronal population activity result in impairment of consciousness? The corollary of this is that a full understanding of the action of anesthetic drugs is somewhat in the domain of “big science,” requiring a synthesis of expertise in the fields of organic chemistry, ion channel kinetics, cellular neuroscience, systems neuroscience, network topology, and behavioral biology (fig. 1).

In the accompanying article, Meyer addresses one of the *how* questions. He postulates that anesthetic disruption of dendritic function could explain how a multiplicity of different molecular effects at the level of the neuron could translate into the observed anesthetic-induced loss of signaling from higher order, more anterior, association cortical regions—the loss of so-called top-down feedback.^{2,3} In essence, he presents



“The model [described also elegantly] explains why different classes of drugs ... might cause the final common behavioral state of ... loss of consciousness.”

an argument that microscale suppression of apical dendritic conduction prevents top-down signaling, disrupting predictive processes; which, in turn, are themselves necessary prerequisites for the conscious state. It is a very cortex-centric argument, and he reviews data emphasizing the idea that perception—and probably consciousness itself—is primarily constructed within a functioning cortex and not generated as a reaction to sensory input. The model also explains why different classes of drugs, which act on a range of different receptors (*e.g.*, γ -aminobutyric acid, *N*-methyl-D-aspartate, hyperpolarization-cyclic nucleotide, calcium), might cause the final common behavioral state of anesthetic loss of consciousness. His approach draws heavily on the (elegant but unproven) idea that the behavioral effects of anesthesia are primarily caused by disturbance of information flux in the brain.⁴ He then reviews a number of theories of consciousness that highlight the importance of expectation (and prediction) in the processes of perception. The point being that consciousness arises from a brain that is actively constructing models of reality and comparing them with external input.

This article succinctly brings to the attention of the general readership many of the recent concepts related to anesthesia and consciousness. It follows the commonly accepted format of marshaling an argument from qualitative biological evidence. However, these traditional types of formulations are probably not stringent enough. To make further progress in explaining anesthesia, it is necessary to move beyond the usual discursive biological arguments about what mechanisms might be plausible; to a position of being able to narrow down exactly what mechanisms really are absolutely necessary for the observed phenomenon. This requires that any theory be disprovable and quantitative. The onus should be on any proposer to describe an experiment that would disprove their theory. If we suggest that dendritic malfunction causes loss

Image: A. Johnson.

Corresponding article on page 1415.

Accepted for publication February 22, 2015. From the Department of Anaesthesia, Waikato Clinical School, University of Auckland, Hamilton, New Zealand.

Copyright © 2015, the American Society of Anesthesiologists, Inc. Wolters Kluwer Health, Inc. All Rights Reserved. *Anesthesiology* 2015; 122:1196-7

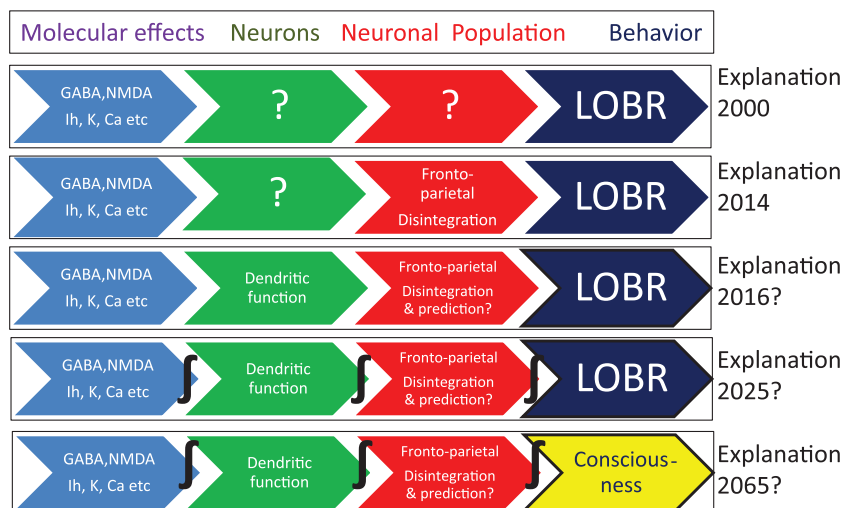


Fig. 1. A cartoon of a possible historical development of a theory of anesthesia. The change, in the *bottom row*, from describing behavior as LOBR to “consciousness,” indicates that the solution of the hard problem has been achieved. Ca = calcium; GABA = γ -aminobutyric acid; Ih = hyperpolarization-activated cyclic nucleotide channel; LOBR = loss of behavioral response; NMDA = *N*-methyl-D-aspartate. The function (f) symbol indicates achievement of a reliable mathematical description of the relationship between scales.

of consciousness, I would suggest that an experiment that showed ongoing consciousness in the presence of dendritic malfunction would disprove the theory. The problem with the, more abstractly framed, predictive coding aspect of this article is that it seems to be undisprovable. The evidence presented consists mainly of electrophysiological studies. There are huge problems in assuming that syntactic information theory applies to actual semantic information processing within the brain; and even more problems with assuming that information flow correlates with scalp electroencephalogram signals. Finally, there is the proverbial elephant in the room—the infamous “hard problem” of consciousness.⁵ As a profession, we have largely ignored this issue or sidestepped the mind–body question by claiming consciousness is all an illusion. It is the ultimate “how” question. Exactly how might “minimization of sensory predictive error” or “hierarchical predictive coding” actually cause the subjective sensation of selfhood that underlies consciousness? If we think of consciousness as the “what it is like to be” for a particular organism,⁶ the hard problem is concerned with how any given physical process could actually produce such a subjective experience. How does a physical process produce a feeling? If we accept the hypothesis of Meyer as being true, and we link “hierarchical predictive coding” to consciousness, there are some inescapable logical corollaries that must follow. For example, we are then required to attribute consciousness whenever we see “hierarchical predictive coding” in action. For example, if this predictive coding was implemented in a computer, it should necessarily make that computer self-aware. This hard problem is indeed hard or even insoluble and will likely keep philosophers, neuroscientists, and anesthesiologists busy for decades to come.

The other serious deficiency in most theories of consciousness is that they are not even approximately quantitative. As

an example, if we were to apply a quantitative approach to the work by Meyer, we should be able to determine exactly *how much* microscale suppression of apical dendritic conduction is required to disrupt predictive processes. Probably completely new mathematical methods and concepts will have to be developed. Eventually a proper theory of anesthesia will require formal mathematical statements (possibly even equations) that can link synaptic and ion channel drug effects with patterns of neuronal population information flow and clinical behavior (and perhaps even consciousness) and thus make possible a robust scientific basis for the clinical titration of anesthesia.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

Correspondence

Address correspondence to Dr. Sleight: jamie.sleight@waikatodhb.health.nz

References

1. Meyer K: The role of dendritic signaling in the anesthetic suppression of consciousness. *ANESTHESIOLOGY* 2015; 122:1415–31
2. Lee U, Ku S, Noh G, Baek S, Choi B, Mashour GA: Disruption of frontal-parietal communication by ketamine, propofol, and sevoflurane. *ANESTHESIOLOGY* 2013; 118:1264–75
3. Mashour GA: Top-down mechanisms of anesthetic-induced unconsciousness. *Front Syst Neurosci* 2014; 8:115
4. Alkire MT, Hudetz AG, Tononi G: Consciousness and anesthesia. *Science* 2008; 322:876–80
5. Långsjo JW, Revonsuo A, Scheini H: Harnessing anesthesia and brain imaging for the study of human consciousness. *Curr Pharm Des* 2014; 20:4211–24
6. Nagel, T: What is it like to be a bat? *Phil Rev* 1974; 83:435–50