Anesthesiology 2010; 113:1007–9

This Is No Humbug

Anesthetic Agent-induced Unconsciousness and Sleep Are Visibly Different

EVER since 1846, when Boston dentist William Thomas Green Morton, in front of a group of skeptical surgeons, administered diethyl ether to a patient about to undergo a surgical operation, we have known that clinical anesthesia is no humbug, and we have been interested in its mechanism of action. In this issue of ANESTHESIOLOGY, Boveroux *et al.*[1] provide some exciting new data that shed some light on this long-standing question.

How Can We Study the Mechanism of Anesthesia?

General anesthesia is a drug-induced, reversible condition comprising five behavioral states: hypnosis (loss of consciousness), amnesia, analgesia, immobility (no movement in response to pain stimuli), and hemodynamic stability with control of the stress response. It is obvious that these five components of anesthesia cannot be studied in parallel in a single study because different models are required to investigate the mechanism of each anesthesia-related state. The current work focuses on loss of consciousness. Traditional approaches to studying the mechanisms of action of general anesthetics focus primarily on characterizing the binding properties of anesthetic drugs to receptor sites in the brain and spinal cord (for review, see Forman *et al.*[2]). These studies have helped identify common molecular and pharmacological principles that underlie anesthetic drugs. They have also been important for establishing that there are several mechanisms of anesthetic action rather than just one. However, molecular studies are not sufficient to understand the functional consequences of anesthetics on specific neuronal pathways in the intact brain.

How Does Functional Magnetic Resonance Imaging Work and Why Do We Use it to Study Mechanism of Anesthesia?

The current study used human brain imaging to visualize neuronal activity throughout the brain while subjects move from the awake to the anesthetized state. The specific technique was functional magnetic resonance imaging (fMRI), a type of specialized MRI scan. In this MRI, the contrast is blood deoxyhemoglobin, thus the MRI image is "blood oxygen level–dependent" (BOLD). The interpretation of fMRI-BOLD data relies on the assumption that changes in neuronal activity are paralleled by characteristic changes in cerebral blood oxygen levels. In the so-called resting state (when subjects are not engaged in sensory, motor, or cognitive tasks), functional networks can be detected by temporally correlating spontaneous activity in different brain regions. This type of analysis operationally defines a network as a group of brain regions (nodes) with correlated hemodynamic activity. An example of one such network is the Default Mode Network, a set of areas encompassing, in the current article, brainstem, thalamus, posterior cingulate/precuneus, medial prefrontal cortex, superior frontal sulci, bilateral temporoparietal junctions, and parahippocampal and temporal cortices.

It is important to understand that a network is defined by functional rather than anatomic connectivity, although the latter is clearly a prerequisite for the former. The concept of functional connectivity has deep historical roots in the work of Hebb *et al.*[3] In the cerebral cortex, where each neuron is hard-wired to thousands of others, the flow of information is governed largely by the state of activity of the neurons—the networks are dynamic. Pharmacological decreases in network connectivity would be expected to disrupt normal brain function. Sometimes activity between networks is inversely or anticorrelated. For example, activity in the network involved in daydreaming may decrease activity when one pays attention to a task, and *vice versa*. Anesthetic-induced decreases or reversals in such anticorrelations would also disrupt normal brain function. Anesthetics could potentially mediate unconsciousness by disrupting thalamocortical con-

◆ This Editorial View accompanies the following article: Boveroux P, Vanhaudenhuyse A, Bruno M-A, Noirhomme Q, Lauwick S, Luxen A, Degueldre C, Plenevaux A, Schnakers C, Phillips C, Brichant J-F, Bonhomme V, Maquet P, Greicius MD, Laureys S, Boly M: Breakdown of within- and between-network resting state functional magnetic resonance imaging connectivity during propofol-induced loss of consciousness. ANESTHESIOLOGY 2010; 113:1038–53.

Accepted for publication July 5, 2010. 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.

nectivity (similar to what we believe happens during sleep), within cortical connectivity, or both.

Functional connectivity can be studied by a variety of techniques, including fMRI-BOLD and electroencephalography, and to our knowledge, all techniques used to reflect neural activity have limitations. fMRI-BOLD–derived connectivity analysis relies on the assumption that neural activity translates to local blood flow changes, and electroencephalographic analysis implies that surface electrodes provide an adequate spatial resolution of neural activity in different parts of the brain.

What Does Propofol-induced Unconsciousness Look Like?

Boveroux *et al.*[1] performed fMRI-BOLD imaging in healthy human volunteers during the following four states: awake, lightly sedated, deeply sedated (not fully anesthetized), and recovered from sedation induced by the anesthetic drug propofol. They detail a number of propofol dose-dependent changes in correlations and anticorrelations that could underlie anesthetic-induced loss of consciousness. They found decreased functional connectivity within certain thalamocortical and higher association corticocortical networks and even the appearance of an anticorrelation at the highest dose. By contrast, they observed preserved connectivity, even during deep sedation, in low-level sensory cortices (*i.e.*, in auditory and visual networks). Thus, it is clear, based on the fMRI connectivity analysis, that there is a more specific action going on than a global reduction in cortical arousal.

At first glance, these anticorrelations seem to fit with thalamic mechanism of anesthesia[4]; a high BOLD signal in the thalamus was associated with low BOLD in the cortex.[1] However, propofol has differential effects on blood vessel tone, independent of neural activity, and it is therefore possible that the observed BOLD-derived anticorrelation simply reflects propofol's differential effects on cerebral blood flow. In fact, propofol decreases cerebral blood flow in the thalamus, whereas it increases blood flow in other parts of the brain, including the hippocampus,[5] an area that generates some of the largest slow-wave (θ) electroencephalogram signals of any brain structure. In addition, the selectivity of the effect on thalamocortical connectivity in higher-order associative *versus* sensory cortices makes it unlikely that a propofol-mediated inhibition of general thalamocortical relay pathways is the main mechanism to mediate a decrease in global cortical arousal. In other words, the paradoxical relation between signs of thalamic activation and cortical deactivation does not seem to be a key contributing mechanism of propofol-induced unconsciousness.

What Is the Difference between Propofol-induced Unconsciousness and Sleep?

Evidence suggests that propofol-induced unconsciousness is mediated by a different mechanism than sleep, a suggestion that is perhaps not surprising based on the obvious clinical and distinct electroenecephalographic[6,7] differences between these states.

Boveroux *et al.*[1] do not report, during propofol-induced unconsciousness, any significant derangement of the networks, *per se*. They observed a linear correlation between functional connectivity and consciousness across most cortical areas of the networks examined. No particular nodes appeared or disappeared. This is in contrast to findings during sleep; Horvitz *et al.*[8] reported that the frontal cortex became uncoupled from the rest of the default mode network during deep sleep while maintaining within default network connectivity during anesthesia.

Another significant difference between sleep and anesthesia is the linearity of the latter. At low-sedative doses, anesthetics cause a state similar to drunkenness, with analgesia, amnesia, distorted time perception, depersonalization, and increased sleepiness. At slightly higher doses, a patient fails to move in response to a command and is considered unconscious.[4] Thus, anesthesia effects are graded and progressive; however, the behavioral states of sleep and wake are not. The mutually inhibitory interactions of the sleep-on neurons in the hypothalamus and wake-on-arousal areas form a flip-flop switch that sharpens state transitions and prevents lingering in an intermediate state between sleep and wake,[9] contrasting with the clinical impression of a continuous transition from wakefulness to anesthesia.

Anesthesia and sleep are visibly different, and the hypothesis that general anesthesia and sleep share brain mechanisms has yet to be critically tested. Sleep requires the inhibition of multiple subcortical pathways in the arousal system. An important group of neurons in the ventrolateral preoptical nucleus responds to the neurotransmitter γ-aminobutyric acid and allows sleep to occur by inhibiting several groups of brainstem neurons in the arousal system, including the tuberomammillary nucleus, locus ceruleus, and orexinergic neurons. The idea that general anesthesia also involves inhibition of arousal pathways is enticing but difficult to prove because we cannot rule out that anesthetics work directly on cortical and thalamic targets, thus making brainstem effects irrelevant. Nonetheless, there may be a dose-dependent anesthetic engagement of an endogenous sleep-state control system. Low doses of anesthetic agents promote ventrolateral preoptical nucleus activity. However, we do not know if the anesthetic agents evoking c-fos (a gene whose expression is related to and a marker for neuronal activity) expression in the ventrolateral preoptical nucleus represents an epiphenomenon or if it is the cause of anesthesia-associated unconsciousness. While it is possible to reverse both sleep and sedation to some extent by stimulating arousal pathways, injection of anesthetics in arousal-promoting neurons in the tuberomammillary nucleus does not provide anesthesia. In conclusion, no convincing evidence exists proving that sleep pathways are necessary for general anesthesia-associated unconsciousness.

What Do We Have to Learn in Future Studies?

The study of Boveroux *et al.*[1] has limitations. The use of fMRI to study the mechanism of anesthesia relies on the assumption that changes in blood flow reflect changes in neuronal activity. However, cerebrovascular confounds pose a serious challenge to interpreting fMRI data during general anesthesia. Inhaled anesthetics are potent cerebral vasodilators, increasing cerebral blood flow by 20–40% at anesthetic concentrations required to produce unconsciousness, potentially saturating the fMRI-BOLD response. Simultaneous electroencephalography and fMRI of general anesthesia represents a promising new approach to separate hemodynamic effects of anesthetics from those directly associated with their neuronal effects (see Brown *et al.*[10]). In addition, general anesthesia-induced hypoventilation increases predictably arterial and tissue carbon dioxide concentrations, which in turn increases cerebral blood flow. Changes in carbon dioxide concentration as small as 5 mmHg produce fMRI-BOLD signal increases similar in magnitude to those seen during task activity. The authors are to be commended for having controlled for these confounders as well as reasonably possible. They measured arterial carbon dioxide and found increased values from baseline only at the highest propofol dose given and regressed out possible global signal effects from their MRI region of interest time-course analysis. The ultimate method of excluding any bias of anesthetic agent–induced hypercapnia on BOLD measurements might be to maintain normocapnia in the volunteers by using noninvasive pressure-support ventilation.

Boveroux *et al.*[1] are to be applauded for taking an important step toward a better understanding of the specific aspects of anesthetic agent–induced unconsciousness.

Nancy L. Chamberlin, Ph.D.,* Matthias Eikermann, M.D., Ph.D.† *Beth Israel Deaconness Medical Center, and Harvard Medical School, Boston, Massachusetts. †Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts. meikermann@partners.org

References

1. Boveroux P, Vanhaudenhuyse A, Bruno M-A, Noirhomme Q, Lauwick S, Luxen A, Degueldre C, Plenevaux A, Schnakers C, Phillips C, Brichant J-F, Bonhomme V, Maquet P, Greicius MD, Laureys S, Boly M: Breakdown of within- and between-network resting state functional magnetic resonance imaging connectivity during propofol-induced loss of consciousness. ANESTHESIOLOGY 2010; 113:1038–53
2. Campagna JA, Miller KW, Forman SA: Mechanisms of actions of inhaled anesthetics. N Engl J Med 2003; 348: 2110–24
3. Morris RG: D.O. Hebb: The organization of behavior, Wiley: New York; 1949. Brain Res Bull 1999; 50:437
4. Alkire MT, Hudetz AG, Tononi G: Consciousness and anesthesia. Science 2008; 322:876–80
5. Byas-Smith M, Frölich MA, Votaw JR, Faber TL, Hoffman JM: Cerebral blood flow during propofol induced sedation. Mol Imaging Biol 2002; 4:139–46
6. Rechtschaffen A, Kales A. A Manual of Standardized Terminology, Techniques, and Scoring System for Sleep Stages of Human Subjects. US Department of Health, Education, and Welfare Public Health Service—NIH/NIND; 1968.
7. Kochs E, Bischoff P, Pichlmeier U, Schulte am Esch J: Surgical stimulation induces changes in brain electrical activity during isoflurane/nitrous oxide anesthesia. A topographic electroencephalographic analysis. ANESTHESIOLOGY 1994; 80:1026–34
8. Horovitz SG, Braun AR, Carr WS, Picchioni D, Balkin TJ, Fukunaga M, Duyn JH: Decoupling of the brain's default mode network during deep sleep. Proc Natl Acad Sci USA 2009; 106:11376–81
9. Lu J, Sherman D, Devor M, Saper CB: A putative flip-flop switch for control of REM sleep. Nature 2006; 441:589–94
10. Purdon PL, Pierce ET, Bonmassar G, Walsh J, Harrell PG, Kwo J, Deschler D, Barlow M, Merhar RC, Lamus C, Mullaly CM, Sullivan M, Maginnis S, Skoniecki D, Higgins HA, Brown EN: Simultaneous electroencephalography and functional magnetic resonance imaging of general anesthesia. Ann NY Acad Sci 2009; 1157:61–70