Uncovering the neurobiological basis of general anesthesia

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The use of general anesthesia is a routine part of surgical operations at hospitals and medical facilities around the world, but the precise biological mechanisms that underlie anesthetic drugs' effects on the brain and the body are only beginning to be understood. A review article in the December 30 *New England Journal of Medicine* brings together for the first time information from a range of disciplines, including neuroscience and sleep medicine, to lay the groundwork for more comprehensive investigations of processes underlying general anesthesia.

"A key point of this article is to lay out a conceptual framework for understanding general anesthesia by discussing its relation to sleep and coma, something that has not been done in this way before," says Emery Brown, MD, PhD, of the Massachusetts General Hospital (MGH) Department of Anesthesia, Critical Care and Pain Medicine, lead author of the NEJM paper. "We started by stating the specific physiological states that comprise general anesthesia – unconsciousness, amnesia, lack of pain perception and lack of movement while stable cardiovascular, respiratory and thermoregulatory systems are maintained – another thing that has never been agreed upon in the literature; and then we looked at how it is similar to and different from the states that are most similar – sleep and coma."

After laying out their definition, Brown and his co-authors – Ralph Lydic, PhD, a sleep expert from the University of Michigan, and Nicholas Schiff, MD, an expert in coma from Weill Cornell Medical College – compare the physical signs and electroencephalogram (EEG)

patterns of general anesthesia to those of sleep. While it is common to describe general anesthesia as going to sleep, there actually are significant differences between the states, with only the deepest stages of sleep being similar to the lightest phases of anesthesia induced by some types of agents.

While natural sleep normally cycles through a predictable series of phases, general anesthesia involves the patient being taken to and maintained at the phase most appropriate for the procedure, and the phases of general anesthesia at which surgery is performed are most similar to states of coma. "People have hesitated to compare general anesthesia to coma because the term sounds so harsh, but it really has to be that profound or how could you operate on someone?" Brown explains. "The key difference is this is a coma that is controlled by the anesthesiologist and from which patients will quickly and safely recover."

In detailing how different anesthetic agents act on different brain circuits, the authors point out some apparently contradictory information – some drugs like ketamine actually activate rather than suppress neural activity, an action that can cause hallucinations at lower doses. Ketamine blocks receptors for the excitatory transmitter glutamate, but since it has a preference for receptors on certain inhibitory neurons, it actually stimulates activity when it blocks those inhibitors. This excess brain activity generates unconsciousness through a process similar to what happens when disorganized data travels through an electronic communication line and blocks any coherent signal. A similar mechanism underlies seizure-induced unconsciousness.

Brown also notes that recent reports suggest an unexpected use for ketamine – to treat depression. Very low doses of the drug have rapidly reduced symptoms in chronically depressed patients who had not responded to traditional antidepressants. Ketamine is currently being

studied to help bridge the first days after a patient begins a new antidepressant – a time when many may be at risk of suicide – and the drug's activating effects may be akin to those of electroconvulsive therapy.

Another unusual situation the authors describe is the case of a brain-injured patient in a minimally conscious state who actually recovered some functions through administration of the sleep-inducing drug zolpidem (Ambien). That patient's case, analyzed previously by Schiff, mirrors a common occurrence called paradoxical excitation, in which patients in the first stage of general anesthesia may move around or vocalize. The authors describe how zolpidem's suppression of the activity of a brain structure called the globus pallidus – which usually inhibits the thalamus – stimulates activity in the thalamus, which is a key neural control center. They hypothesize that a similar mechanism may underlie paradoxical excitation.

"Anesthesiologists know how to safely maintain their patients in the states of general anesthesia, but most are not familiar with the neural circuit mechanisms that allow them to carry out their life-sustaining work," Brown says. "The information we are presenting in this article – which includes new diagrams and tables that don't appear in any anesthesiology textbook – is essential to our ability to further understanding of general anesthesia, and this is the first of several major reports that we anticipate publishing in the coming year."

Schiff adds, "We think this is, conceptually, a very fresh look at phenomena we and others have noticed and studied in sleep, coma and use of general anesthesia. By reframing these phenomena in the context of common circuit mechanisms, we can make each of these states understandable and predictable."

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