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Using Anesthesia to Reveal the Elements of Consciousness

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Abstract

General anesthesia provides an invaluable experimental tool to probe the essential neural circuits that underlie consciousness. A new study reports that cholinergic stimulation of the prefrontal cortex restores wake-like behaviors in anesthetized rodents, suggesting that cholinergic inputs to the prefrontal cortex play a fundamental role in modulating consciousness.

The essential neural circuits that generate consciousness are unknown. There are multiple subcortical pathways that promote arousal, but the cortical areas that modulate arousal states are not well understood. In a recently published study, Pal and colleagues [1] reported that cholinergic stimulation of the prefrontal cortex (PFC), but not the parietal cortex, restores wake-like behaviors in rats anesthetized with sevoflurane. The authors also found that noradrenergic stimulation of these areas was insufficient to induce wake-like behaviors under the same anesthetic regimen. These results suggest that cholinergic inputs to the PFC are critically important in regulating levels of consciousness.

In the context of natural sleep, numerous subcortical arousal pathways in the brain have been identified. Cholinergic neurons in the brainstem and basal fore-brain, noradrenergic neurons in the locus coeruleus, histaminergic neurons in the tuberomammillary nucleus, and others are known to decrease sleep and increase wakefulness. However, it has become increasingly evident that not all arousal circuits are capable of inducing emergence from the anesthetized state. Dopamine reuptake inhibitors such as methylphenidate and dextroamphetamine, as well as optogenetic stimulation of ventral tegmental area dopamine neurons [2], have been shown to induce wake-like behaviors in anesthetized rodents, while reuptake inhibitors that are selective for norepinephrine are ineffective [3]. The latter finding is consistent with the report by Pal *et al.* that norepinephrine administration in neither the PFC nor parietal cortex promotes wake-like behaviors during sevoflurane anesthesia. While noradrenergic neurotransmission is thought to be important for the transition to wakefulness from natural sleep, noradrenergic stimulation appears insufficient to induce wake-like behaviors during continuous general anesthesia.

Despite the notable lack of behavioral changes, the authors found that noradrenergic stimulation of the PFC and parietal cortex nevertheless produced wake-like changes in the

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electroencephalogram that were similar to those observed with cholinergic stimulation of the same areas. This result is also consistent with the finding that intravenous administration of a norepinephrine reuptake inhibitor during sevoflurane anesthesia produces wake-like electroencephalogram changes without behavioral changes indicative of wakefulness [3]. This dissociation has important implications for the future design of neurophysiological monitors that utilize the cortical electroencephalogram to determine anesthetic depth in surgical patients.

General anesthetics have been used clinically for more than 170 years, and their molecular sites of action have been largely established. Unconsciousness is the *sine qua non* of general anesthesia, but it is now apparent that different general anesthetics have distinct molecular mechanisms of action that lead to the same endpoint of unconsciousness [4]. Some (e.g., propofol and barbiturates) primarily act by enhancing inhibitory GABAergic neurotransmission, while others (e.g., ketamine and nitrous oxide) mainly inhibit excitatory glutamatergic neurotransmission. Halogenated volatile anesthetics such as isoflurane and sevoflurane represent a unique class of non-selective drugs that modulate several relevant molecular targets including GABA_A receptors, glutamate receptors, and two-pore domain potassium channels.

Although volatile anesthetics are perhaps the least well understood in terms of their underlying mechanisms of action, they are particularly well suited for neural circuit studies of consciousness. This is because a stable concentration of anesthetic in the brain can be readily achieved by fixing the inhaled concentration of the anesthetic at a constant dose, allowing investigators to test neural circuit manipulations under consistent experimental conditions. Even though intravenous anesthetics are more selective for their molecular targets, achieving steady-state concentrations of intravenous drugs in the brain is far more difficult due to the added complexities introduced by drug redistribution and metabolism. One important question that remains difficult to answer is whether the same neural circuit manipulations restore consciousness in the setting of different general anesthetics that have distinct molecular targets.

Pal *et al.* demonstrated that the level of consciousness is increased with cholinergic stimulation of the PFC, which raises an intriguing question: what is the content of consciousness for these animals? In other words, are they experiencing arousal in the absence or presence of awareness? Is memory intact? Of course, these questions are challenging to address with animal studies, but future experiments that use cognitive tasks may lead to further insights.

Technological advances that allow for selective manipulation of neuronal subpopulations *in vivo* have opened the door to answering many questions in neuroscience, including the mystery of how and where anesthetics act at the level of neural circuits and systems to induce unconsciousness. Indeed, there is growing evidence that these drugs act at discrete neural circuits to produce their profound effects. For example, microinjection of anesthetics into a discrete portion of the upper brainstem can produce a state akin to general anesthesia [5], and isoflurane has been found to activate sleep-promoting neurons in the ventrolateral preoptic area [6]. Surprisingly, it was recently reported that excitatory glutamatergic neurons

in the lateral habenula play a critical role in the sedative actions of propofol [7]. Anesthetic drugs also directly affect thalamo-cortical and cortico-cortical pathways [8], leaving us to ponder whether general anesthetics produce unconsciousness by acting in a ‘bottom-up’ manner that targets subcortical circuits to decrease arousal, or in a ‘top-down’ manner that targets cortical neurons to disrupt higher-order neural networks [9]. When general anesthetics are systemically administered, both mechanisms likely contribute to the unconscious state.

Much work is still needed to elucidate the fundamental neural circuits that regulate consciousness. Recent advances in neuroscience provide an unprecedented opportunity for scientists and clinicians to work synergistically to advance knowledge in this area. Deciphering the building blocks of consciousness will not only advance neuroscience but also lead to progress in the medical care of thousands of patients who undergo general anesthesia for surgery every day, by refining neurophysiological monitoring devices and possibly generating novel approaches to induce reversible unconsciousness. In addition, elucidating these essential neural circuits will likely lead to better care for brain-injured patients suffering from disorders of consciousness, by improving tools for prognostication and therapy [10]. It is exciting to envision how advances in neuroscience today will shape the operating rooms and intensive care units of tomorrow.

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