Scientists identify brain cells that drive wakefulness and resist general anesthetics

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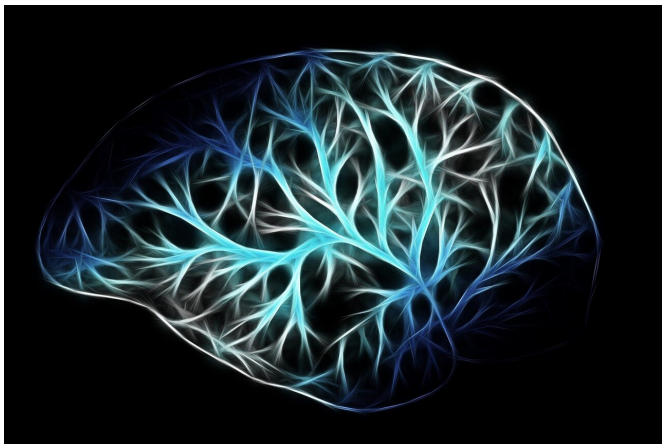

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Neuroscientists don't know precisely what brain circuits control wakefulness and sleep, nor exactly how drugs for general anesthesia affect those circuits. But a new study from Penn Medicine researchers brings neuroscience a step closer to solving that important conundrum.

A team of researchers from the Perelman School of Medicine at the University of Pennsylvania, in a study published online Nov. 13 in *Current Biology*, identified a population of neurons in the hypothalamus region of the brain that keeps mice from sleeping when they normally would when they are activated. Activating these neurons also "wakes" them from ongoing exposure to inhaled anesthetics like isoflurane or sevoflurane, and even helps maintain the alert state when animals are dosed with anesthetics.

The study also supports a hypothesis long debated by neuroscientists: that the parts of the brain regulating sleep and waking are also capable of regulating the brain's response to general anesthetics.

"Our findings add to evidence that the neural circuits regulating wakefulness may also be important for the exit from general anesthesia," said study senior author Max Kelz, MD, PhD, the Anesthesia Distinguished Professor at the Perelman School of Medicine at the University of Pennsylvania.

The findings point to the possibility of future pharmaceuticals to actively speed the exit from anesthetic states and could also promote wakefulness that might be useful in neurologic diseases such as narcolepsy. In patients with the capacity to recover from minimally conscious states, therapeutics that engage strong wake-promoting systems could offer novel therapeutic strategies to coax the brain back to a state of conscious wakefulness.

Kelz and colleagues, including the first author of the study, PhD candidate Sarah Reitz, focused on a region of the hypothalamus known as preoptic area (POA). Prior studies had yielded conflicting findings about which populations of POA neurons contribute to sleep, wakefulness, and anesthesia. However, spurred by recent findings that previously targeted populations of POA neurons are actually much more diverse on the molecular level than had been assumed, the Penn Medicine team examined one recently identified sub-population that express the tachykinin 1 gene, known as POA Tac1 neurons.

The scientists genetically engineered mice in which POA Tac1 neurons—and only those neurons—could be switched "on" for a few hours by giving the animals an injection of a harmless chemical called CNO.

"We found that activating the mice's POA Tac1 neurons sharply increased the wakefulness of those mice compared to the control mice," Reitz said. By using electroencephalography, or EEG, the researchers observed that in a period when the mice normally would be spending most of their time

sleeping, control mice, on average, fell asleep within a few minutes of receiving an injection of an inert chemical, spending only about 40 percent of the four-hour recording session asleep. However, the CNO-injected, POA Tac1-activated mice stayed awake for nearly the entire session, experiencing only a few, brief periods of sleep. At times when the mice were active, the POA Tac1-activated mice also had much longer intervals of wakefulness compared to the control mice.

In further experiments, the researchers found that these same POA Tac1 neurons could promote wakefulness against general anesthetics—drugs that are used to keep patients in an unconscious state during major surgery. Compared to normal conditions, switching on POA Tac1 neurons increased the amount of anesthetic required to induce an unconscious state. Moreover, when these neurons were activated, mice emerged from both isoflurane- and sevoflurane-induced anesthetic states at doses that had previously kept them unconscious.

Remarkably, inhibiting POA Tac1 neurons instead of activating them had no effect on natural sleep or anesthesia-induced unconsciousness—suggesting that these neurons may be "quiet" under many conditions or that, while they are sufficient to produce wakefulness, these POA Tac1 neurons may not be always required for wakefulness. The researchers continue to study POA hypothalamic neurons to tease apart the sub-populations responsible for different sleep- and wake-related functions.

"Now that we understand the potential power of these POA Tac1 neurons, we are starting to study their firing patterns in animals as they naturally cycle through states of sleep and wakefulness, as well as enter or exit states of general anesthesia," said Kelz. "We wonder whether poorly timed resumption of firing in these or other wake-promoting neurons might ultimately be responsible for the rare one in a thousand cases in which anesthetized patients inappropriately regain consciousness during their surgical procedures."

More information: Sarah L. Reitz et al. Activation of Preoptic Tachykinin 1 Neurons Promotes Wakefulness over Sleep and Volatile Anesthetic-Induced Unconsciousness, *Current Biology* (2020). DOI: 10.1016/j.cub.2020.10.050

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