

Researchers identify neural circuitry responsible for rousing the brain during sleep apnea

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A common and potentially serious sleep disorder, obstructive sleep apnea affects at least one quarter of U.S. adults and is linked to increased risk of diabetes, obesity and cardiovascular disease. In a paper published today in the journal *Neuron*, researchers at Beth Israel Deaconess Medical Center (BIDMC) identified specific neural circuitry responsible for rousing the brain of mice in simulated apnea conditions. The findings could lead to potential new drug therapies to help patients with obstructive sleep apnea get more rest.

Often but not always marked by loud snoring, sleep apnea occurs when a sleeping person's airway collapses and closes off breathing. Dipping oxygen (O₂) levels and rising carbon dioxide (CO₂) levels in the blood alert the sleeping brain to the problem, rousing the sleeper just long enough to re-establish breathing.

"A person with apnea wakes up and starts breathing again and this cycle can repeat hundreds of time per night, so the person never gets very deeply asleep," said senior author Clifford B. Saper, MD, Chair of the Department of Neurology at BIDMC. "In the morning, they may not remember that they have not had a restful night's sleep but will feel very tired."

Fragmented sleep can leave people with apnea with significant impairments to cognition, mood and daytime alertness; it may

also increase cardiovascular risk. But what if scientists could prevent the brain from rousing itself hundreds of times per night in response to rising CO₂ levels, while allowing it to reestablish regular respiration again?

“Our goal was to identify the circuitry responsible for waking the brain up during sleep apnea, which is distinct from the part of the brain that controls breathing,” said Saper, who is also the James Jackson Putnam Professor of Neurology and Neuroscience at Harvard Medical School. “If we could keep the brain from waking up during apneas and activate only the part of the brain that opens up the airways, people with obstructive sleep apnea would still be able to get a good night’s rest.”

Using an enclosure with adjustable atmospheric levels of O₂ and CO₂, Saper and colleagues mimicked the effects of OSA in mice by changing the ratio of the two gases every five minutes for 30 seconds.

Then, Saper and colleagues focused on a subset of neurons – called PBel^{CGRP} cells– known to show activity in response to elevated CO₂ levels. The team used mice with these cells genetically-altered in such a way that researchers could activate or suppress the neurons at will using light or drugs to trigger genetic switches. Known as optogenetics and chemogenetics, these experiments demonstrated that activating these cells will wake mice up and keep them up for hours. They also showed that suppressing PBel^{CGRP} cells’ activity would let mice sleep even as CO₂ levels in the air around them rose. Taken together, these findings show that the PBel^{CGRP} cells wake up the brain and are necessary for arousal.

In the final experiment, the researchers followed the PBel^{CGRP} neurons’ long-reaching branches (called axons) to the cells they connect with in other regions of the brain. Without

disrupting the cells' entire activity, the researchers switched off PBel^{CGRP} neurons' connection to a key site in the basal forebrain. That resulted in a nearly complete loss of sensitivity to CO₂ arousal.

Saper and colleagues note that rising CO₂ levels may not be the only factor that repeatedly rouses people with sleep apnea throughout the night. Negative air pressure in the collapsed upper airway may also send "wake-up" messages to the brain via another neuronal circuit. Or PBel^{CGRP} neurons may rouse a sleeping brain in response to a variety of stimuli, not just rising CO₂ levels, the researchers suggest. Learning which neurons regulate arousal could allow scientists to develop drugs to treat obstructive sleep apnea and other sleep disorders.

"The long-term goal of this research is to come up with drugs that will affect specific pathways in the brain," Saper said. "The next step is to see if we can use drugs to prevent the wake-up response while augmenting the opening of the airway. That way, having an apnea won't wake a person up."

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