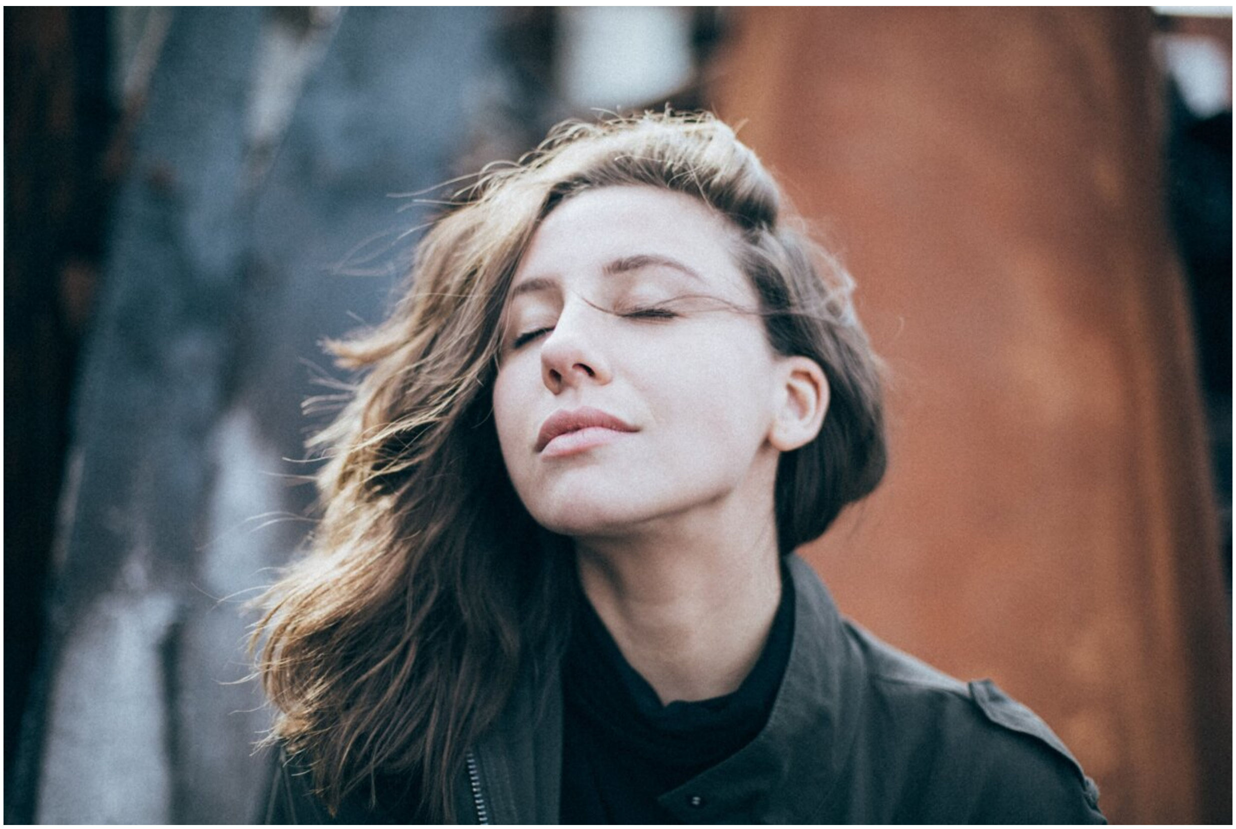
Study in mice reveals how the body copes with airway closure

March 6 2024



Credit: Unsplash/CC0 Public Domain

There is perhaps no bodily function more essential for humans and other mammals than breathing. With each breath, we suffuse our bodies with oxygen-rich air that keeps our organs and tissues healthy and working properly—and without oxygen, we can survive mere minutes.

But sometimes, our breathing becomes restricted, whether due to infection, allergies, exercise, or some other cause, forcing us to take deep, gasping breaths to quickly draw in more air.

Now, researchers at Harvard Medical School have identified a previously unknown way in which the body counteracts restricted breathing—a new reflex of the vagus nerve that initiates deep breathing. Their work is published March 6 in *Nature*.

The research, conducted in mice, reveals a rare and mysterious cell type in the lungs that detects airway closure and relays the signal to the vagus nerve—the information highway that connects the brain to almost every major organ. After the signal reaches the brain, a gasping reflex is initiated that helps the animal compensate for the lack of air.

"Our airway sensations are some of our most vital and powerful for survival, but a lot of the neural pathways within the airways are poorly understood. We found a fundamental pathway for how the body monitors lung openness and the efficiency of the respiratory system to control breathing," said lead author Michael Schappe, a research fellow in neurobiology at HMS.

Although the research remains to be confirmed in humans, these findings provide valuable insight into how the brain and body are connected to monitor and modulate respiration—and could offer a starting point for understanding what happens when respiration goes wrong.

The mystery of orphan neurons

Study senior author Stephen Liberles, professor of cell biology in the

Blavatnik Institute at HMS, is broadly interested in how the brain and body work together to control various physiologic functions, including how the brain processes information from internal organs, senses infections such as influenza, and suppresses nausea.

As Schappe, Liberles, and their team began investigating the respiratory system, they realized there are many different types of neurons in the lungs, but little is known about what some of these neurons actually do.

"We were excited by the idea that these mysterious 'orphan neurons' could be involved in body-brain reflexes that have remained hidden and uncharacterized," Liberles said.

In the 1860s, scientists discovered the Hering-Breuer reflex, which protects the lungs from over-inflation. This reflex occurs when neurons in the lungs detect that the airway is being stretched and quickly signal the body to exhale and breathe less deeply.

The researchers suspected that there might be a second, inverse respiratory reflex that occurs when neurons sense that the airway is getting restricted, lung volume is reduced, and the body needs to take in more air. The resulting sensation of breathlessness or air hunger, Liberles said, can be distressing, yet little is known about how it arises.

A reflex to guard against air hunger

To test whether such a reflex existed, Schappe led a series of experiments in mice that involved restricting their breathing and recording their physiologic reactions, as well as the response of neurons in their lungs. The team also used genetic tools to activate and deactivate the lung neurons to see how this activity or inactivity affected respiration.

When mice experienced airway closure, they reflexively gasped for air. The researchers noticed that a particular subgroup of vagal sensory neurons was more active during this gasping behavior. When the researchers deactivated the neurons, the mice no longer gasped for air in response to airway closure. When the neurons were activated, the animals gasped even in the absence of airway restriction.

This finding points to a dedicated reflex through the vagus nerve that gets activated by airway closure and leads to gasping, Liberles said.

Next, the researchers examined how these neurons prompt a gasping reflex. They observed that the neurons sit in the lining of the respiratory tract and have a distinct chandelier-shaped structure. Each "arm" of the neuron leads to a cluster of cells called neuroepithelial bodies, or NEBs, which, according to Liberles, "are very poorly studied and have been a mystery since they were first discovered in the lungs."

Further experiments showed that NEBs were necessary for the gasping reflex, and sufficient to cause it. The team discovered that NEBs expressed a force-sensing protein called PIEZO2 that is also involved in sensing touch in the skin, and that disabling PIEZO2 eliminated the gasping reflex.

"We found an airway closure-activated reflex that is the companion of the Hering-Breuer reflex," Liberles said. "This new reflex involves a very different neuron structure in the lungs and resolves the long-standing mystery of what NEBs are doing."

More unknowns ahead

NEB cells have been linked to certain human diseases that cause decreased lung function, but it was unexpected to find a connection between NEBs and the pathway through the vagus nerve that senses a reduction in lung volume, Schappe said.

The findings, the researchers noted, highlight how much there is to learn about NEBs, including their role in disease.

Next, the researchers are interested in solving another mystery: PIEZO2 is classically known to be activated by stretch, not constriction, so they want to know how airway closure changes the lung forces around NEBs to activate the protein.

The team is also interested in studying the remaining orphan neurons in the lungs and airways to understand what they are sensing and whether they are involved in other undiscovered respiratory reflexes.

The study falls firmly in the realm of basic research, but it provides an important first step towards more fully understanding the respiratory system in humans, who have many of the same genes and cell types, including sensory receptors, as mice.

"We want to understand the functions of these neurons and what they control physiologically so that ultimately we can figure out how they translate into internal sensations experienced by humans," Schappe said.

More information: Stephen Liberles, A vagal reflex evoked by airway closure, *Nature* (2024). DOI: 10.1038/s41586-024-07144-2. www.nature.com/articles/s41586-024-07144-2

Provided by Harvard Medical School