Breathless: How blood-oxygen levels regulate air intake

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Credit: George Hodan/public domain

Researchers have unraveled the elusive process by which small, highly vascular clusters of sensory cells in the carotid arteries "taste the blood," as a 1926 essay put it—the initial step in regulating blood-oxygen levels.

In the April 21 issue of the journal *Science Signaling*, a University of Chicago-based research team describes the precise mechanism that cells in the carotid bodies use to detect oxygen levels in the blood as it flows toward the brain. The cells translate that taste test into signals, sent through the carotid sinus nerve, a branch of the glossopharyngeal nerve, to stimulate or relax breathing rates.

"After a lengthy search, one that began almost 90 years ago, we were able to identify the long-sought oxygen sensor," said study senior author Nanduri Prabhakar, PhD, director of the Center for Systems Biology of Oxygen Sensing at the Institute of Integrative Physiology of the University of Chicago. "In the process, we also discovered that it has a back-up system."

The primary blood-oxygen sensor is the enzyme heme oxygenase-2. "This is the critical molecule," Prabhakar said. "It is a crucial component of this process."

When blood is adequately oxygenated, heme oxygenase-2 induces synthesis of the gaseous messenger carbon monoxide. This carbon monoxide initiates a chain of events. It stimulates production of cyclic guanosine monophosphate, activating protein kinase G. Protein kinase G then adds a phosphate group to the enzyme, cystathionine-&Upsih;-lyase (CSE), blocking the generation of hydrogen sulfide, another gas messenger. Inactivating CSE prevents the carotid body from sending out a nerve signal to increase air intake.

"When oxygen levels fall, there is no heme oxygenase-2 activity, and no production of carbon monoxide," Prabhakar said. The carotid bodies instead produce abundant hydrogen sulfide by cystathionine-&Upsih;-lyase, which activates nerve signals. This increases breathing, heart rate and blood pressure. "Hydrogen sulfide goes up," he said, "as oxygen level goes down."

The researchers, seeking to confirm their initial finding, next examined mice that lacked the gene for heme oxygenase-2. This led them to a parallel inhibitory system. Mice that lacked heme oxygenase-2 did not produce carbon monoxide, but showed an "unanticipated compensatory increase" of a different oxygen-sensitive enzyme. This one—neuronal nitric oxide synthase—increased production of nitric oxide. The nitric oxide acts like carbon monoxide through protein kinase G to attach a phosphate group to a particular site of CSE, which silenced neural output.

The presence of two closely related mechanisms with a single purpose emphasizes the importance of carotid body oxygen sensing. This alternative system of oxygen sensing provides "an important fail-safe redundancy for a vital homeostatic process," the authors wrote.

While adequate oxygen in the blood inhibits nerve signals, an oxygen shortage—caused by stresses such as exercise, lung disease, sleep apnea or thin air at high altitudes—sets off an alarm, promptly sending the signal to breathe to the central nervous system.

Understanding the detection and signaling mechanisms used by the carotid bodies "is of fundamental significance," said Prabhakar. An inadequate response to hypoxia can lead to serious consequences, such as hypertension and pulmonary edema at high altitude.

There is also a growing sense that a malfunction of gaseous messenger interactions could lead to other disorders.

"It is becoming increasingly recognized that abnormal gaseous signaling contributes to diverse diseases, including Parkinson's disease," Prabhakar said. "Heme oxygenase-2, neuronal nitric oxide synthase, and cystathionine-&Upsih;-lyase are all expressed in neurons as well as in the vasculature. Irregular crosstalk between these messengers may contribute

to the pathophysiology of other disorders. A significant excess or deficiency of this system may result in the death of cells, tissue or the entire organism."

More information: "Protein kinase G-regulated production of H2S governs oxygen sensing," *Science Signaling*, 2015.

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