Hemoglobin Molecule's Secret Revealed

Intrigued by a paradox, Duke University researchers recently revisited one of life's deepest mysteries: how red blood cells carry oxygen to tissues and cart off carbon dioxide waste.

Now, the scientists report in the March 21 NATURE, they have solved both the paradox—how blood vessels dilate even though red blood cells are filled with a potent vasoconstrictor, hemoglobin—and the larger mystery.

They have discovered an elusive component of hemoglobin's dynamic respiratory cycle that enables the substance not only to exchange oxygen for carbon dioxide but also to control blood pressure.

The component is what a member of the Duke team, biochemist Joseph Bonaventura, calls a near "mirror image" of the well-known oxygen–carbon dioxide cycle. The process relies on nitric oxide, a chemical synthesized in the lungs and blood vessel walls, to dilate blood vessels and ensure that oxygen-rich hemoglobin can penetrate even the narrowest capillaries to nourish tissues.

"We have discoveries here that I know will hold true and change the way that people think," says Jonathan S. Stamler of Duke University Medical Center in Durham, N.C. "This has major implications for diseases of every organ."

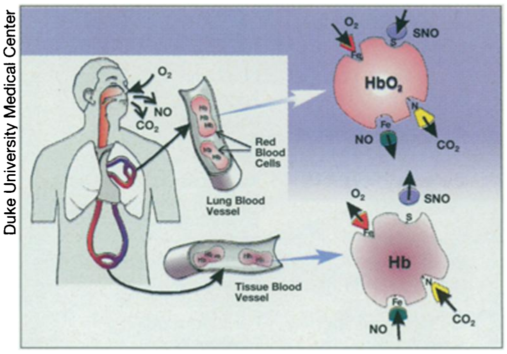
Scientists say the discoveries could lead quickly to an effective blood substitute and new ways of treating ailments that involve blood and tissue oxygenation, including heart attack, stroke, and sickle-cell anemia.

Researchers have long known that nitric oxide from blood vessel walls relaxes and dilates the vessels. Oxygenated hemoglobin was thought to act as a scavenger, rapidly eliminating nitric oxide from the blood. Yet somehow, enough nitric oxide remains to dilate the vessels, helping hemoglobin to make its vital rounds.

There was another loose end as well—literally. A single amino acid, cysteine, dangles from the hemoglobin molecule, and for 50 years researchers have wondered why. They have suspected that this cysteine must be useful because it is present in mammals and many birds.

The Duke team believes it has the explanation. Bonaventura says that the cysteine residue enables nitric oxide to ride safely on the hemoglobin molecule.

Duke University Medical Center



In the lungs, hemoglobin (Hb) binds nitric oxide (NO) as S-nitrosothiol (SNO). In tissue, this SNO is released, and free, circulating nitric oxide is bound to a different site for exhalation.

"In essence, it means that hemoglobin is carrying its own vasodilator," asserts Austen Riggs of the University of Texas at Austin.

Robert Furchgott of the State University of New York Health Science Center at Brooklyn, called the Duke insight "a new idea, surprising and interesting to those of us who have been using hemoglobin as a scavenger."

In essence, the Duke researchers say, the complete hemoglobin respiratory cycle—now recognized as the interplay of oxygen, carbon dioxide, and nitric oxide—works like this: In the lungs, nitric oxide latches onto hemoglobin's cysteine residue when the oxygen binds to hemoglobin's iron. The nitric oxide on the hemoglobin is part of a chemical group called a thiol. Blood with the enriched hemoglobin then circulates through the body.

Because the nitric oxide is sheltered as part of a thiol, circulating hemoglobin cannot degrade it. As the hemoglobin transfers its oxygen to tissues, it also sheds small amounts of nitric oxide, which dilates the blood vessels and helps get the oxygen into tissues.

Next, depleted hemoglobin picks up carbon dioxide and any circulating nitric oxide and carries both to the lungs, where they are exhaled.

"They have made a case for a very different behavior of hemoglobin," Furchgott says. "Now it will have to be looked at more carefully."

"It is inevitable in science that when you have a discovery like this it will be challenged," Stamler says. "But we can make buckets of [hemoglobin] with nitric oxide on the thiol and oxygen on the heme [iron group]. The dogma says that's impossible." —*S. Sternberg*

Solar forecast: Looking for the max

Like fashion trends, the sun goes through cycles, with its behavior shuttling between the conservative and the flamboyant. During the wilder phase, known as a solar maximum, the sun's energetic activity can cause major problems, from harming satellites to disrupting electrical power grids here on Earth.

Although the sun reached record levels of activity during recent solar cycles, a team of researchers now predicts calmer behavior for the next peak, expected in the year 2000. On average, each solar cycle lasts 11 years.

"This is some good news. It's a fairly benign cycle. This should give a little bit of a break to satellites," says Kenneth Schatten, a solar physicist at NASA's Goddard Space Flight Center in Greenbelt, Md. Schatten and his colleagues published their prediction in the March 15 GEOPHYSICAL RESEARCH LETTERS.

The sun is currently passing through a quiet period, or solar minimum, with reduced numbers of sunspots and electromagnetic storms. Schatten and his coworkers use observations of the sun's magnetic field during this tranquil part of the cycle to forecast behavior during the next solar maximum.

With this so-called precursor method, Schatten's team predicts that the peak of the next solar cycle, number 23, will have a mean sunspot index of 138, although this figure has a wide margin of error. The last solar maximum, in September 1989, had a sunspot index of 157.5, and the last four cycles have averaged near 150.

Scientists and engineers monitor solar forecasts to plan for problems that can arise during periods of unusually strong activity. The sun emits the most ultraviolet radiation at these times, heating and expanding Earth's upper atmosphere. The swollen atmosphere exerts increased friction on low-flying satellites, such as the Hubble Space Telescope, and can eventually drag them out of their orbits.

Schatten has scored better than most forecasters with his predictions of the last two solar cycles. However, his model, like all the others, suffers because it does not simulate the basic physical processes generating the solar cycle.

"That may change in the next 5 years," says Ernest Hildner of the National Oceanic and Atmospheric Administration's Space Environment Center in Boulder, Colo. New satellites and ground-based networks are expected to grant scientists much better observations of the sun in coming years, which brightens the outlook for future solar forecasts. —*R. Monastersky*