PICK YOUR POISON

CO IS GOOD FOR YOU (IN SMALL AMOUNTS)

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Carbon monoxide. When we think about it, we tend to think of cars coughing up exhaust or maybe a poorly vented kerosene heater. It's a leading cause of fatal poisoning.

Yet the deadly gas is actually produced in small doses by our bodies.

And in minute amounts, carbon monoxide can be therapeutic. If your body produces more of the gas, you're likely to heal more quickly from injuries. Some researchers are hoping to one day administer it to patients in need.

"What I find interesting about carbon monoxide is that it still has a little bit of a shock value that you're using what's really thought of as a lethal gas for beneficial effects," says the University of Pittsburgh's Brian Zuckerbraun, an assistant professor of surgery.

Zuckerbraun is among a handful of researchers actively investigating the anti-inflammatory effects of carbon monoxide. He says his work is heavily influenced by research conducted by Augustine Choi and Leo Otterbein. In the mid-1990s, those scientists were investigating the beneficial effects of heme oxygenase-1 enzymes—which break down to form carbon monoxide as one of their byproducts—for preventing injury from different types of insults.

The two researchers, then at Johns Hopkins University, discovered that blocking the enzymes led to more cell damage.

"I came up with the hypothesis that carbon monoxide was the mechanism by which the enzyme heme oxygenase-1—which was known to be protective and which Dr. Choi and I had studied for years prior—was functioning," says Otterbein.

This idea became the focus of Otterbein's doctoral dissertation and, later, his research concentration when he and Choi moved to Yale University. Shortly after they published a *Nature Medicine* paper in 2000 that showed carbon monoxide had anti-inflammatory effects in mice and in mouse cell cultures, the scientists relocated to Pitt.

At the time, Zuckerbraun, then a surgery fellow, was working on nitric oxide—another gas notorious for its toxicity and later found to be beneficial in small quantities within the body. He soon joined Choi and Otterbein's research efforts.

Now Zuckerbraun runs his own lab, with carbon monoxide as a main area of investigation. (In 2004, Otterbein left Pitt to join the faculty at Harvard Medical School. Choi recently accepted a position there as well.)

Zuckerbraun studies pulmonary hypertension, i.e., high blood pressure in the arteries supplying blood to the lungs.

By the time symptoms of the disorder present themselves, the damage is typically irreversible. Patients end up short of breath from even low levels of exertion and can't perform simple functions such as walking up the stairs.

In end-stage cases, the only treatment is lung transplantation. No therapies are available to reverse the artery thickening that causes high blood pressure.

Zuckerbraun is interested in how carbon monoxide might help those with the disorder.

He's exploring using carbon monoxide to reverse thickening of blood vessels in the lung by encouraging protective genes and restoring damaged cells to health.

The surgeon also investigates how inhaling the gas could protect against injuries of other organs and hemorrhagic shock.

"If you could deliver controlled doses of carbon monoxide, you could potentially prevent inflammation that takes place as a result of the hemorrhage and the consequences of that," says Zuckerbraun.

In cases such as hemorrhagic or septic shock, our tissues don't get enough oxygen. When inhaled in large quantities, carbon monoxide is poisonous—entering the bloodstream where its molecules bind to oxygen-carrying hemoglobin and essentially suffocating the body by starving it of oxygen at the cellular level. Doctors have known that since the 19th-century French physiologist Claude Bernard poisoned dogs to learn about the toxic effects of carbon monoxide.

Yet Bernard had only half the story. The gas doesn't always reduce oxygen levels in tissues. In fact, in some circumstances, it can lead to increased oxygen levels, says Zuckerbraun.

And he and Otterbein suggest it's likely that carbon monoxide is helpful during shock states to limit and regulate oxygen consumption in the setting of decreased oxygen delivery to organs and cells.

Carbon monoxide also acts as a signaling molecule within the cell. "For instance, in Brian's work," says Otterbein, "nitric oxide is deficient in pulmonary hypertension."

"We need nitric oxide, driven by carbon monoxide, [to decrease the thickness of artery walls].

"So in that case, the target of carbon monoxide is the enzyme that makes nitric oxide synthase. We believe that carbon monoxide influences that enzyme directly to make more nitric oxide."

Pick your poison. Now scientists have shown us two—nitric oxide and carbon monoxide—required to keep people healthy. ■