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Team designs molecule that could be first antidote for carbon monoxide poisoning

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Researchers from the University of Pittsburgh School of Medicine and UPMC have engineered a protein that reverses carbon monoxide (CO) poisoning in mice, a discovery that could potentially lead to the creation of the first antidote in humans to the often deadly poisoning, according to research published today in the journal *Science Translational Medicine*.

CO poisoning is responsible for more than 50,000 emergency room visits in the United States annually, and is one of the leading global causes of poisoning death. A colorless, odorless gas, CO is extremely effective at replacing oxygen molecules in hemoglobin, the oxygen carrying protein in blood. CO exposure also results in debilitating effects on the body and the brain, including cognitive deficits that in some cases can persist months or years after a poisoning event.

"Despite being the most common poisoning worldwide, we still do not have an effective antidote for CO exposure," said Mark T. Gladwin, M.D., chair of medicine, Pitt School of Medicine, Dr. Jack D. Myers Professor of Internal Medicine, and director of the Pittsburgh Heart, Lung, Blood and Vascular Medicine Institute. "Our protein is extraordinarily effective at scavenging CO from the blood, and could potentially prove to be a significant advance in the treatment of CO poisoning."

Current treatment options for CO poisoning—administering 100 percent oxygen or using a pressurized hyperbaric chamber to administer oxygen at greater than normal air pressure—focus on trying to replace CO in

blood with oxygen as quickly as possible. However, both these treatments are only moderately effective. Moreover, transporting patients to a hyperbaric chamber requires a significant amount of time, and many poisoned patients may not be stable enough for this therapy.

When studying neuroglobin (Ngb), a hemoglobin-like protein present in the brain, Gladwin and his team discovered it could bind CO with an unusually high affinity. Based on prior knowledge of how the protein works, researchers engineered a mutant version of the protein, called Ngb H64Q, that was an even better scavenger of CO.

In a purified sample of red blood cells infused with CO, they found that Ngb H64Q was 1,200 times faster at forcing CO to release itself from being bound to hemoglobin than just air alone. When tested in a mouse model of non-lethal CO poisoning, they found that Ngb H64Q was significantly better at removing CO from hemoglobin than 100-percent oxygen treatment. The normal half-life of CO in humans after poisoning (time it takes for half of the CO to be eliminated from the body) is 320 minutes, and even with 100-percent oxygen therapy, that time is 74 minutes. With the antidote therapy, the CO half-life was reduced to only 23 seconds.

In a mouse model with lethal levels of CO poisoning, seven out of eight mice treated with Ngb H64Q (87.5 percent) survived the duration of the experiment, while 10 percent or less survived in the control groups. Additionally, the antidote restored blood pressure and improved the amount of oxygen that was present in tissues, suggesting that Ngb H64Q works by scavenging CO from hemoglobin and allowing oxygen to bind in its place, thus restoring normal oxygen delivery.

Importantly, CO bound to Ngb H64Q was detected in the urine of mice shortly after treatment, which indicated that the rodents were able to excrete the antidote from the body without any major toxic effects.

"If approved, this antidote could be rapidly administered to victims in the field, eliminating costly delays that occur with current treatment options," Gladwin said. "We still need extensive safety and efficacy testing before an antidote is available on the shelf, but our early results are very promising."

Researchers plan to scale up their safety and efficacy testing in animal models and hope to advance to clinical trials within the next few years.

More information: "Five-coordinate H64Q neuroglobin as a ligand-trap antidote for carbon monoxide poisoning," *Science Translational Medicine*, stm.sciencemag.org/lookup/doi/ … scitranslmed.aah6571

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