Study identifies possible role for carbon monoxide in treating hemorrhagic stroke

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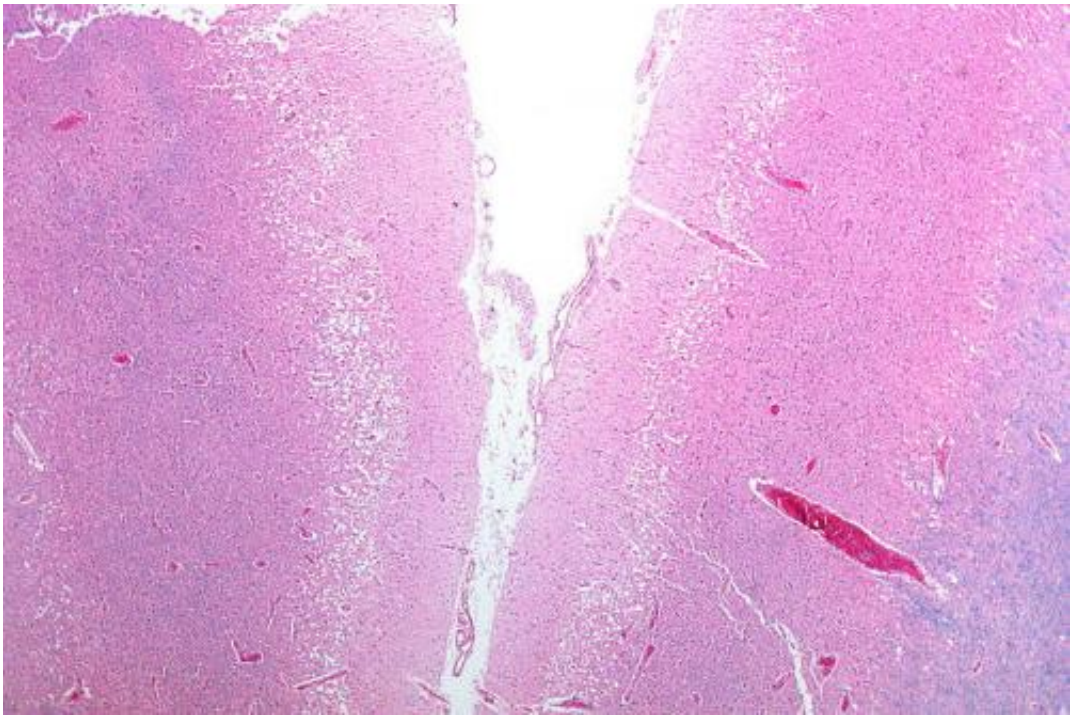

Micrograph showing cortical pseudolaminar necrosis, a finding seen in strokes on medical imaging and at autopsy. H&E-LFB stain. Credit: Nephron/Wikipedia

Carbon monoxide is known by many as a poisonous gas that causes brain injury and other neurological symptoms, including memory loss and confusion. But a new study led by investigators at Beth Israel Deaconess Medical Center (BIDMC) suggests the opposite may be true: When administered in small, carefully controlled amounts, carbon monoxide

may actually protect the brain from damage following subarachnoid hemorrhage, a devastating stroke that results from bleeding in the brain.

Published online today in *The Journal of Clinical Investigation* (JCI), the new findings show that carbon monoxide can help accelerate a natural process that minimizes cognitive damage by speeding the clearance of heme, a highly toxic component of red blood cells that can accumulate and cause brain inflammation following hemorrhagic stroke.

"Aneurysmal subarachnoid hemorrhage [SAH] affects about 40,000 individuals in the U.S. each year," explained co-senior and corresponding author Khalid A. Hanafy, MD, PhD, Neurological Director of the Neurointensive Care Unit at BIDMC and Assistant Professor of Neurology at Harvard Medical School (HMS). "SAH is a terrible condition that begins with a catastrophic headache, which patients describe as being like a bomb exploding in their heads."

SAH is a type of stroke that develops as the result of an aneurysmal rupture that coats the exterior of the brain in blood. It predominantly affects women between the ages of 45 and 55 and has a 50 percent mortality rate within 12 months of onset. Thirty to 40 percent of surviving SAH patients suffer long-term cognitive damage.

In this new work, Hanafy teamed with co-senior author Leo E. Otterbein, PhD, an investigator in the Transplant Institute at BIDMC and Associate Professor of Surgery at HMS who has investigated the therapeutic applications of carbon monoxide for more than 15 years. Otterbein's novel studies have revealed a number of promising therapeutic applications for the gas, including treatment of pulmonary hypertension, prevention of organ rejection following transplantation, reduction of vascular restonsis, shrinkage of cancerous tumors and infection-fighting abilities.

"My laboratory has been studying the properties of carbon monoxide for years, but we've never investigated a possible therapeutic role for CO in the brain," said Otterbein. "As a neurologist specializing in intensive care medicine, Dr. Hanafy was very interested in subarachnoid hemorrhage and was already investigating mechanisms by which heme caused inflammation in the brain following stroke. It was this natural multidisciplinary collaboration between our laboratories that helped lead to this exciting paradoxical discovery."

The findings hinge on a group of brain cells called microglia. "Microglia can have many different functions, but in this work, we found that they were acting as something of a 'trash collector' for the brain," explained Hanafy.

One of the principal components in the "trash" that piles up following SAH is a pigment called heme, which is found in the hemoglobin protein within red blood cells. When red blood cells become damaged, as is the case in hemorrhagic stroke, the heme pigment is released from the protein and ventures outside the confines of the red blood cell where it becomes highly injurious, causing inflammation and death to surrounding brain tissue.

"In their trash-collecting capacity, microglia remove the heme using an enzyme called heme oxygenase-1 [HO-1]," said Hanafy, adding that this critical function is accomplished, in large part, through the generation of carbon monoxide.

"What appears to be happening is that HO-1 in the microglia removes the heme burden from the extracellular space and rapidly transforms it into iron, bile pigments and carbon monoxide," added Otterbein.

After determining that CO was the protective element observed with HO-1, the researchers went on to test whether safe, modest levels of

inhaled CO could help mitigate brain damage following SAH. They created a mouse model of SAH and exposed one group of mice to normal air and a second group to one hour of inhaled CO gas per day for seven days following the onset of subarachnoid hemorrhage.

The mice then underwent a series of maze experiments to test cognitive abilities. "The mice that were exposed to CO performed substantially better," said lead author Nils Shallner, PhD, a research fellow in the Otterbein lab and investigator at the University Medical Center Freiburg, Germany. "This told us that CO could improve functional outcome following a hemorrhagic stroke."

"Both neuronal injury and cognitive function were restored when we treated the mice with safe, low amounts of carbon monoxide," added Hanafy. "Moreover, this occurred even when HO-1 was missing. In other words, CO therapy effectively substituted for the lack of endogenous CO generated by HO-1."

The new findings offer an important avenue for future clinical research and development of CO-based therapies for the treatment of patients with ruptured cerebral aneurysms and provide compelling data that—in carefully controlled amounts—CO can protect the brain.

"Much of the CO toxicity that has been described over the years focuses on adverse neurological effects such as confusion, nausea and headache that likely result from exposure to very high levels of CO as well as to hundreds of other toxic molecules that are found in combustion products, such as auto exhaust," said Hanafy. "Our investigations lay the groundwork for future clinical trials to test CO in patients with SAH. In the future, we could potentially provide a therapeutic option for a devastating disease that primarily strikes women in their 40s and 50s."

"We have been asking the same question for years: Why would the body

naturally produce CO if it was inherently toxic to cells?" added Otterbein. "In this collaborative work, our teams were able to show that a small dose of CO can offer neurological protection and that it is the production of CO by HO-1 that helps to prevent brain damage following hemorrhagic stroke."

Provided by Beth Israel Deaconess Medical Center