'Hibernation-on-demand' drug significantly improves survival after extreme blood loss

1 July 2008

For the first time, researchers have demonstrated that the administration of minute amounts of inhaled or intravenous hydrogen sulfide, or H2S – the molecule that gives rotten eggs their sulfurous stench – significantly improves survival from extreme blood loss in rats.

Cell biologist Mark B. Roth, Ph.D., and colleagues in the Basic Sciences Division of Fred Hutchinson Cancer Research Center, in collaboration with surgeon Robert K. Winn, Ph.D., and colleagues at UW Medicine's Harborview Medical Center, report their findings online ahead of print in *The Journal of Trauma Injury, Infection, and Critical Care*. The article is slated for the July print issue, which comes out on July 10.

The researchers successfully used H2S to induce a state of reversible metabolic hibernation as a way to reduce death from insufficient blood supply to organs and tissues in a rat model of lethal hemorrhage. (Federal regulations mandate the use of such animal models in preclinical research to test the safety and effectiveness of various procedures and treatments before they can be tested in humans.)

They found that 75 percent of rats (18 of 24) given inhaled hydrogen sulfide and 67 percent of rats (eight of 12) given intravenous hydrogen sulfide survived at least two weeks – the duration of the monitoring period – after losing more than half of their blood for an extended period. In contrast, long-term survival rates for the untreated rats in the two control groups were 23 percent (three of 13) and 14 percent (one of seven), respectively.

"Our goal is to develop life-saving treatment for critically ill people suffering from acute, sustained blood loss, such as in a car accident or on the battlefield," said senior author Roth. "These findings have obvious implications for the military, but they also have tremendous implications for the civilian population."

The U.S. Defense Advanced Research Projects Agency and the U.S. Defense Services Office funded the research. The ultimate goal: designing self-injectable hydrogen-sulfide kits that critically injured soldiers could use in the field to temporarily dim their metabolism and reduce their oxygen demand. This would help "buy time" until they could get medical attention.

"The military feels that if a soldier can be kept alive for at least three hours, that would allow time for the situation to be stabilized and the scene of the incident secured enough to allow evacuation of that soldier to an area where he or she can get medical attention," Roth said.

Roth's study, which attempted to mimic a similar scenario, involved 56 rats, each of which underwent controlled hemorrhage to remove 60 percent of their blood for three hours before re-infusion with Lactated Ringer's solution to replace lost blood volume.

The rats were divided into two groups. In the first group, 24 rats were put into a controlled atmosphere of room air laced with 300 parts per million H2S while 13 served as controls. The H2S was administered about 20 minutes after initiation of blood removal and was supplied for about 20 minutes, until the end of the bleed. In the second group, 12 rats received a single intravenous dose of sulfide solution about 20 minutes after the initiation of blood removal while seven served as controls.

In both test groups, the rats maintained a reduced yet stable level of carbon-dioxide production, a surrogate measure of metabolism. Once H2S was removed, metabolic rates returned to normal. In contrast, the untreated animals steadily grew metabolically weaker from blood loss until the point of death.

Functional and behavioral testing among the long-

term survivors (those that lived more than two weeks after hemorrhage) showed no observable defects. In fact, the rodents that were bred produced normal-sized litters of healthy pups.

How does hydrogen-sulfide treatment prevent death from profound and sustained blood loss? One possibility is that in reducing metabolism, H2S also reduces oxygen demand, which allows crucial neurons in the hippocampus, the part of the brain that controls autonomic functions such as breathing and heartbeat, to withstand low oxygen levels due to hemorrhage.

Another mechanism may be that hydrogen sulfide, which is naturally present in the blood, is lost during hemorrhage and must be replaced to maintain life processes.

In April 2005 Roth and colleagues made headlines worldwide when they reported, in the journal Science, the first use of H2S to induce a state of reversible hibernation in mice. Roth's latest research represents the next step in demonstrating hydrogen sulfide's potential to treat ischemic injuries caused by conditions such as severe blood loss, hypothermia, cardiac arrest and stroke.

Source: Fred Hutchinson Cancer Research Center