Could hydrogen sulfide hold the key to a long life?

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Hydrogen sulfide, or H2S, the chemical that gives rotten eggs their sulfurous stench – and the same compound that researchers at Fred Hutchinson Cancer Research Center successfully have used to put mice into a state of reversible metabolic hibernation – has now been shown to significantly increase life span and heat tolerance in the nematode worm, or C. elegans.

These findings by Mark Roth, Ph.D., a member of the Center's Basic Sciences Division, and Dana Miller, Ph.D., a postdoctoral research fellow in Roth's lab, appear in the PNAS Online Early Edition, a publication of the *Proceedings of the National Academy of Sciences*.

In an effort to understand the mechanisms by which hydrogen sulfide induces hibernation in mice, the researchers turned to the tiny nematode, a workhorse of laboratory science because its biology is similar in many respects that of humans. For example, like humans, nematodes have a central nervous system and the ability to reproduce. The worms also are ideally suited for studying life span, because they normally live for only two to three weeks.

The researchers found, to their surprise, that nematodes that were raised in a carefully controlled atmosphere with low concentrations of H2S (50 parts per million in room air) did not hibernate. Instead, their metabolism and reproductive activity remained normal, their life span increased and they became more tolerant to heat than untreated worms.

The H2S-exposed worms lived eight times longer than untreated worms when moved from normal room air (22 C or 70 F) to a high-temperature environment (35 degrees Celsius, or 95 F). Roth and colleagues replicated these results in 15 independent experiments.

"Although the maximum extension of survival time varied between experiments, the effect was quite robust. On average, 77 percent of the worms exposed to H2S outlived the untreated worms," Roth said. The mean life span of worms grown in an atmosphere laced with hydrogen sulfide was 9.6 days greater than that of the untreated population, a longevity increase of 70 percent.

Most genes that influence life span in C. elegans act on one of three genetic pathways: those that control insulin/IGF (insulin growth factor) signaling, those that control mitochondrial function and those that modulate the effects of dietary restriction.

Roth and colleagues ruled out hydrogen sulfide's influence on each of these pathways. Instead, they suspect it acts through a different mechanism. One theory is that exposure to H2S naturally regulates the activity of a gene called SIR-2.1, which has been shown to influence life span in many organisms, including the nematode. Previous studies have found that over-expression of this gene increases the longevity of C. elegans by 18 percent to 20 percent.

"Further research into the genetic mechanisms that influence H2S-induced changes in nematodes may reveal similar mechanisms in higher organisms, including humans, with potentially wide-ranging implications in both basic research and clinical practice," Roth said. For example, understanding how H2S affects physiology in animals may lead to the development of drugs that could delay the onset of age-related diseases in humans such as cancer, Alzheimer's and heart disease.

Roth's hibernation research made headlines worldwide in April 2005 when he was the first to show that exposing mice to minute amounts of hydrogen sulfide could induce a state of reversible "hibernation on demand," dramatically reducing their core body temperature, respiration and need for oxygen. Roth envisions a future in which similar techniques could be used to "buy time" for critically

ill patients who otherwise would face injury and death from insufficient blood and oxygen supply to organs and tissues.

Roth hypothesizes that H2S, a chemical normally produced in humans and animals, may help regulate body temperature and metabolic activity. Hydrogen sulfide is similar to oxygen at the molecular level because it binds at many of the same proteins. As a result, H2S competes for and interferes with the body's ability to use oxygen for energy production – a process within the cell's power-generating machinery called oxidative phosphorylation.

The inhibition of this function, in turn, is what Roth and colleagues believe causes organisms such as mice to shut down metabolically and enter a hibernation-like state pending re-exposure to normal room air, after which they quickly regain normal function and metabolic activity with no long-term negative effects.

Source: Fred Hutchinson Cancer Research Center