Hydrogen sulfide shows promise as healthy aging therapeutic when specifically targeted within cells

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Future therapies to help people live healthy lives for longer could be developed from drugs that release tiny amounts of the gas hydrogen sulfide (H_2S), new research has indicated.

A study from the University of Exeter found that targeting tiny amounts of H_2S to specific areas of cells in adult worms using a H_2S-releasing molecule called AP39, greatly improved health and activity as they aged.

The research, published in *PNAS*, concludes that targeting H_2S specifically to the energy-generating machinery of cells (mitochondria) could one day be used as a healthy aging therapeutic. The paper is titled, "Mitochondrial sulfide promotes lifespan and healthspan through distinct mechanisms in developing versus adult treated Caenorhabditis elegans."

The research team administered AP39 to some worms from birth, and to others after reaching adulthood. They found that this compound improved the integrity of mitochondria—the "power house" of cells, which produces our cells' energy, and kept the worms' muscles active and moving, even well into old age, and when given mid-way through their life-course.

A number of age-related conditions are linked to loss of mitochondrial function, including natural aging, neurodegenerative diseases such as Parkinson's and Alzheimer's as well as muscular dystrophy and primary mitochondrial diseases.

The team also found a group of proteins that regulated how genes are expressed in aging (transcription factors). There transcription factors were found to be specifically targeted by H_2S. This insight may identify new targets for therapy in aging and age-related conditions, particularly conditions affecting muscle.

Senior author Professor Tim Etheridge, of the University of Exeter, said, "Worms are a powerful genetic tool to study human health and disease and offer a strong platform to quickly identify new potential therapeutics. Diseases related to aging take a huge toll on society. Our results indicate that H_2S, administered to specific parts of the cell in tiny quantities, could one day be used to help people live healthier for longer."

In previous research, the team had found that they could successfully

target skeletal muscle with H_2S in worms, and the new paper represents the first time this technique has been applied to natural aging.

The University of Exeter has assigned the underlying technology to its spin-out MitoRx Therapeutics, which has developed next generation compounds with much better drug characteristics as potential medicines to combat diseases of aging including neurodegenerative disorders such as Huntington's disease as well as rare childhood conditions such as muscular dystrophy.

Co-author Professor Matt Whiteman, from the University of Exeter, said, "This study is not about extending life—it's about living healthier lives well into older age. This could have huge benefits to society. We're excited to see this research move to the next stages over the coming years, and hope it will one day form the basis of new treatments which we have the potential to develop with MitoRx."

"We saw a small extension of lifespan in the worms that were targeted with H_2S, and what's unique here is that we extended healthspan—or the time they lived healthy lives. The worms still died, albeit later than normally expected, but they died very active and with young physiology."

More information: Vintila, Adriana Raluca et al, Mitochondrial sulfide promotes life span and health span through distinct mechanisms in developing versus adult treated Caenorhabditis elegans, *Proceedings of the National Academy of Sciences* (2023). DOI: 10.1073/pnas.2216141120

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