Hydrogen sulfide could guard against Alzheimer's disease

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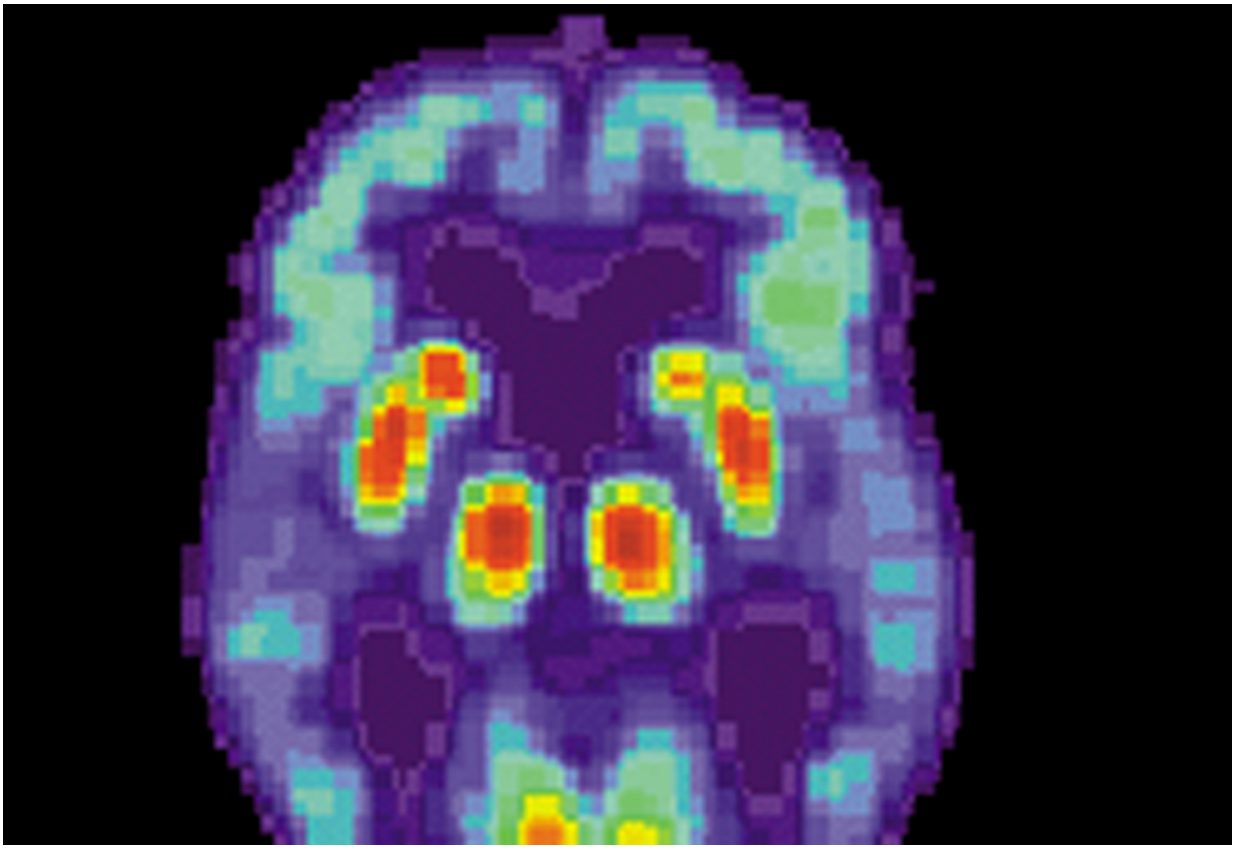


PET scan of a human brain with Alzheimer's disease. Credit: public domain

Typically characterized as poisonous, corrosive and smelling of rotten eggs, hydrogen sulfide's reputation may soon get a facelift. In experiments in mice, researchers have shown the foul-smelling gas may

help protect aging brain cells against Alzheimer's disease. The discovery of the biochemical reactions that make this possible opens doors to the development of new drugs to combat neurodegenerative disease.

The study was led by John Hopkins Medicine, working with the University of Exeter. The findings are reported in *The Proceedings of the National Academies of Science*.

"Our new data firmly link aging, neurodegeneration and cell signaling using hydrogen sulfide and other gaseous molecules within the cell," says Bindu Paul, M.Sc., Ph.D., Faculty Research Instructor in neuroscience in the Solomon H. Snyder Department of Neuroscience at the Johns Hopkins University School of Medicine and lead corresponding author on the study.

The human body naturally creates small amounts of hydrogen sulfide to help regulate functions across the body from cell metabolism to dilating blood vessels. The rapidly burgeoning field of gasotransmission shows that gases are major cellular messenger molecules, with particular importance in the brain. However, unlike conventional neurotransmitters, gases can't be stored in vesicles. Thus, gases act through very different mechanisms to rapidly facilitate cellular messaging. In the case of hydrogen sulfide, this entails the modification of target proteins by a process called chemical sulfhydration, which modulates their activity, says Solomon Snyder, D.Phil., D.Sc., M.D., professor of neuroscience at the Johns Hopkins University School of Medicine and co-corresponding author on the study.

Previous studies using a new method have shown that sulfhydration levels in the brain decrease with age, a trend that is amplified in patients with Alzheimer's disease. "Here, using the same method, we now confirm a decrease in sulfhydration in the AD brain," says collaborator Milos Filipovic, Ph.D., Principal Investigator, Leibniz-Institut für

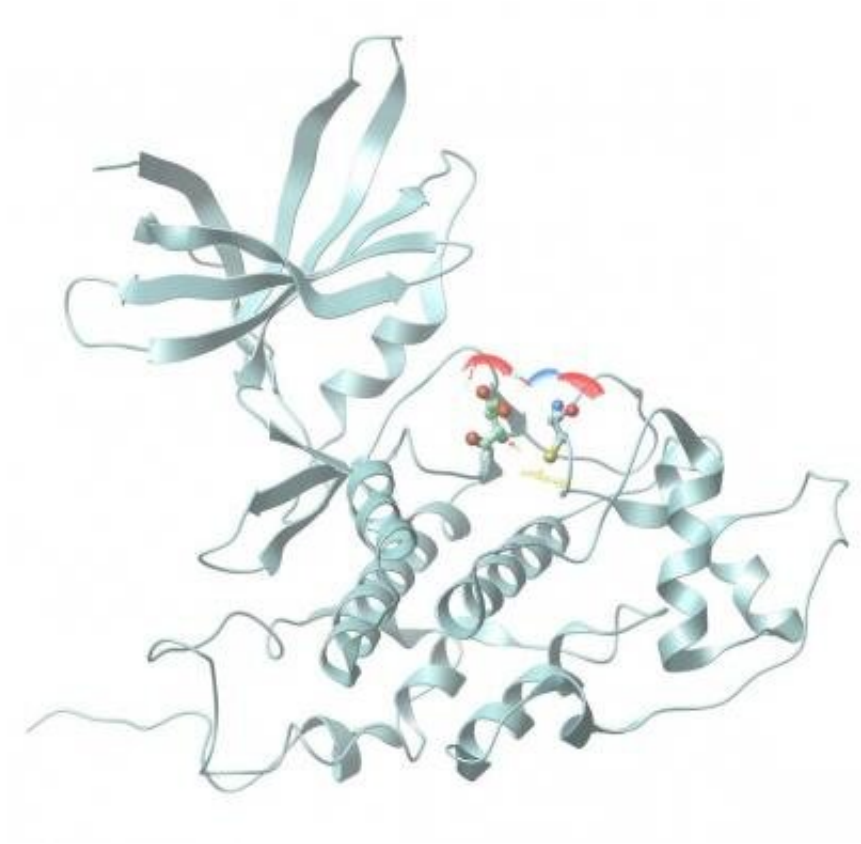
Analytische Wissenschaften—ISAS.

For the current research, the Johns Hopkins Medicine scientists studied mice genetically engineered to mimic human Alzheimer's disease. They injected the mice with a hydrogen sulfide-carrying compound, called NaGYY, developed by their collaborators at University of Exeter, that slowly releases the passenger hydrogen sulfide molecules while traveling throughout the body. The researchers then tested the mice for changes in memory and motor function over a 12-week period.

Behavioral tests on the mice showed that hydrogen sulfide improved cognitive and motor function by 50per cent compared with mice that did not receive the injections of NaGYY. Treated mice were able to better remember the locations of platform exits and appeared more physically active than their untreated counterparts with simulated Alzheimer's disease.

"Up until recently, researchers lacked the pharmacological tools to mimic how the body slowly makes tiny quantities of H2S inside cells. "The compound used in this study does just that and shows by correcting brain levels of H2S, we could successfully reverse some aspects of Alzheimer's disease," says collaborator on the study, Matt Whiteman, Ph.D., Professor of Experimental Therapeutics at the University of Exeter Medical School.

The results showed that the behavioral outcomes of Alzheimer's disease could be reversed by introducing hydrogen sulfide, but the researchers wanted to investigate how the brain chemically reacted to the gaseous molecule.



A ribbon model of a sulfhydrated GSK3β that would inhibit its activity. Oxygen atoms are shown in red, sulfur in yellow and nitrogen in blue. Credit: Bindu Paul and Johns Hopkins Medicine

A series of biochemical experiments revealed a change to a common enzyme, called glycogen synthase β (GSK3β). In the presence of healthy levels of hydrogen sulfide, GSK3β typically acts as a signaling molecule, adding chemical markers to other proteins & altering their function. However, the researchers observed that in the absence of hydrogen sulfide, GSK3β is over-attracted to another protein in the brain, called Tau.

When GSK3β interacts with Tau, Tau changes into a form that tangles and clumps inside nerve cells. As Tau clumps grow, the tangled proteins

block communication between nerves, eventually causing them to die. This leads to the deterioration and eventual loss of cognition, memory and motor function that is characteristic of Alzheimer's disease.

"Understanding the cascade of events is important to designing therapies that can block this interaction like natural hydrogen sulfide is able to do," says Daniel Giovinazzo, M.D./Ph.D. student, the first author of the study.

The Johns Hopkins Medicine team and their international collaborators plan to continue studying how sulfur groups interact with GSK3β and other proteins involved in the pathogenesis of Alzheimer's disease in other cell and organ systems. The team also plans to test novel hydrogen sulfide delivery molecules as part of their ongoing venture.

More information: Daniel Giovinazzo et al. Hydrogen sulfide is neuroprotective in Alzheimer's disease by sulfhydrating GSK3β and inhibiting Tau hyperphosphorylation, *Proceedings of the National Academy of Sciences* (2021). DOI: 10.1073/pnas.2017225118

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