Chronic Fatigue and...Hydrogen Sulfide (H2S)?

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Hypothesis: Chronic Fatigue Syndrome is caused by problems of hydrogen sulfide metabolism and results in mitochondrial dysfunction.

1. Introduction
H2S is a gas which, unlike other gases, has been recognized as a cellular signaling molecule. Recent research has suggested that H2S may play a role in various physiological processes. The introduction of H2S into the body, with many important regulatory roles to play in the IHSS, mitochondrial dysfunction and cellular processes, can result in symptoms of fatigue and other symptoms. This hypothesis suggests that H2S is a natural regulator of mitochondrial function.

2. Objective
I am not looking to make money. Instead, my goal is to interest you in the idea presented here with the hope that you will find it sufficiently compelling to test this hypothesis. Failing that, I hope that you will be curious enough after reading this paper to Google, your favorite search engine, or seek other areas of interest with the keyword “hydrogen sulfide.” This is an emerging field of study, and there are many excellent resources available on this topic.

3. Origin of the Idea
In 2007, I attended a lecture in Washington, D.C., on the role of hydrogen sulfide in the body. I was interested in the research being done on the role of H2S in various physiological processes. The information I learned at that lecture has been the basis for my research on the role of H2S in Chronic Fatigue Syndrome.

4. Hydrogen Sulfide in the Body: the Amount Counts
In the past few years, extensive research has been made in the complex role of hydrogen sulfide in the body, although the mechanisms remain to be elucidated. It is clear, however, that H2S plays a crucial role in cellular metabolism and mitochondrial processes. There are some things that are known about the gas.

- H2S is the first recognized endogenous gas in the body. It is a natural product of the body, released during cell metabolism, both in aerobic and anaerobic conditions. "It is a simple molecule, which may not be involved in the regulation of essential cellular functions."
- H2S is important in the regulation of cellular metabolism. It is involved in the regulation of mitochondrial processes, including the regulation of cellular respiration.

5. Exogenous H2S
H2S is a gas that is produced by aerobic and anaerobic processes. It is produced by the action of certain bacteria, such as the bacterium Desulfovibrio vulgaris, which produces hydrogen sulfide from sulfur compounds.

6. H2S and Mitochondria
Mitochondria are organelles descended from ancient sulfur-metabolizing microbes and display a high affinity for sulfide that permits its use as an energetic substrate at a physiological concentration. Mitochondria are the site of the main oxygen consumption in the body, and the production of ATP is closely related to the oxygen consumption. How H2S may affect the mitochondria and cause CFS:

- H2S enters the energy transport chain of Complex IV, where it binds to the mitochondrial enzyme cytochrome c oxidase.
- This stimulates nitric oxide production and the production of hydrogen sulfide (H2S), which is involved in cellular signaling.

7. Conclusions and Recommendations
There is evidence to suggest that the gas H2S is involved in the regulation of mitochondrial function and cellular processes. Further research is needed to fully understand the role of H2S in the body and its effects on cellular and mitochondrial processes.

Acknowledgments:
I wish to express my gratitude to Carl Pugh, who edited the manuscript, and to all those who provided encouragement and support. This work was supported by a grant from the National Institutes of Health, and I would like to acknowledge the assistance of all those who worked on this project.

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6. H2S and Mitochondria

Mitra fourths and other association with low mitochondrial processes.

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1. Introduction
H2S, the gas which smells like rotten eggs, has long been recognized as a lethal environmental toxin. Recently, we have come to understand that it is also an endogenous signaling “gasotransmitter” within the body, with many important roles to play in the HPA, central nervous and immune systems. It appears to block cells from using oxygen, which may mean that it is a natural regulator of metabolism and energy.

2. Objective
I am not looking for money. Instead, my goal is to interest you in the ideas presented here with the hope that you will find them sufficiently compelling to test this hypothesis. Failing that, I hope that you will be curious enough after reading this poster to “Google” your own particular area of interest with the keywords “hydrogen sulfide”. This is an emerging field of study; H2S may turn out to be the main agonist to oxygen, with important implications in the pathology of many diseases.

Hypothesis: Chronic Fatigue Syndrome is caused by problems of hydrogen sulfide metabolism and results in mitochondrial dysfunction.

Does an increase in H2S inhibit mitochondrial utilization of oxygen? Are our bodies using H2S to seek redox equilibrium, drawing on an ancient capability conserved in the mitochondria to utilize H2S as a substrate to obtain energy? If so, how would a mitochondrial myopathy or enzyme deficiency related to sulfur metabolism affect this proposition? What about an increase in sulfate-reducing or sulfide-producing bacteria?
3. Origin of the Idea:
In 2007, I attended a lecture in Washington, D.C., on the topic of using hydrogen sulfide gas to induce “hibernation” in mice. The scientist, Mark Roth of the Fred Hutchinson Cancer Research Center, described how he had pumped low levels of H2S (80 p.p.m.) into a sealed chamber, sinking mice into a state of “suspended animation”. The mice were in an *apnea sleep-like state* for approximately five hours. He theorized that H2S had “switched off” the cellular need for oxygen.

As I listened to him describe this experiment, I was struck by the similarities in the physiological responses of the mice to the gas and the symptoms experienced by those with CFS:

<table>
<thead>
<tr>
<th>w/ INCREASE in H2S,</th>
<th>w/ INCREASE in O2,</th>
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<tbody>
<tr>
<td>Body Temperature</td>
<td>Returned to Normal</td>
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<td>Heart Rate</td>
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<td>Respiration Rate</td>
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<tr>
<td>Metabolic Rate</td>
<td>Returned to Normal</td>
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Could this have something to do with chronic fatigue, I wondered?
4. Hydrogen Sulfide in the Body: *the Amount Counts*

In the past few years, enormous progress has been made in deciphering the complex role that hydrogen sulfide plays in the body, although the research remains in its infancy. It is clear, however, that H2S plays an important role in cardiovascular, central nervous and gastrointestinal systems. Here are some things that are known about the gas:

-H2S is the first inorganic substrate for human cells.\(^1\) It is a key player in blood pressure regulation,\(^2\) and is also thought to control the availability of nitric oxide in the vascular system.\(^3\)

-H2S decreases adenosine triphosphate levels (ATP) in aortic rings and leads to vasorelaxation via metabolic inhibition, depending upon oxygen levels of the tissue.\(^4\)

-It serves as an oxygen sensor/transducer in vertebrate hypoxic vasodilation.\(^5\) It also binds to hemoglobin in red blood cells, interfering with oxygen transport.

-H2S is reported to be a mediator of cerebral ischemic damage.\(^6\)\(^7\) It is also thought to regulate body temperature.

-In the brain, H2S is produced from l-cysteine via cystathionine beta-synthase (CBS) and cystathionine gamma-lyase (CSE) in response to neuronal excitation, where it alters long term potentiation and initiates calcium waves.\(^8\) It is recognized as a neuromodulator and neuroprotectant.

-H2S regulates calcium homeostasis in microglial cells\(^9\) and intracellular pH in vascular smooth muscle cells.\(^10\)

-Some evidence suggests that H2S can modulate the HPA axis function.\(^11\) It appears to regulate the release of corticotrophin-releasing hormone from the hypothalamus, where it also causes an ATP-sensitive K⁺ channel-dependent decrease in blood pressure in freely-moving rats.\(^12\)

-At certain levels, mice exposed to exogenous gas showed an increase in blood lactate concentration and lactate/pyruvate ratio, leading to anaerobic glycolysis and inhibition of lipid peroxidation.\(^13\)

-H2S plays a pivotal role in both aerobic and non-aerobic organisms as a signaling molecule.\(^14\) Bacteria in the gut both produce H2S and use it as a substrate alternative to oxygen. It has been implicated in both ulcerative colitis\(^15\) and colon cancer. It induces direct radical-associated DNA damage.\(^16\)

-It is a novel mediator of leukocyte activation; it may exert its effect on inflammation via regulating the function of leukocytes, leukocyte trafficking and immune cell survival.\(^17\)

-Exogenous H2S induces functional inhibition and cell death of cytotoxic lymphocyte subsets of CD8 (+) T cells and NK cells, depending upon intracellular glutathione levels.\(^18\)

-Whole tissue hydrogen sulfide concentrations are orders of magnitude lower than presently accepted values.\(^19\)

-Many foods and substances can produce H2S (see side panel).

5. Exogenous H2S

-H2S is a basic element in the natural world (volcanoes, sulfur springs, natural gas deposits, deep sea vents, bacteria etc.). It is increasing in the atmosphere as a result of human activity; crude oil refineries, natural gas processing plants, pulp and paper mills, sewage treatment plants, large hog and other farms (CAFOs), tanneries, sulfur and coke processing, rayon facilities, landfills, and many other industrial and chemical processes produce hydrogen sulfide.
6. H2S and Mitochondria

Mitochondria are organelles descended from ancient sulfur-metabolizing microbes and display a high affinity for sulfide that permits its use as an energetic substrate at low micromolar concentrations. If the supply of sulfide exceeds the oxidation rate and poisoning renders mitochondria inefficient, one would expect cells to shift to anaerobic mechanisms, a shift that has been reported in CFS patients.

How H2S may affect the mitochondria and cause CFS:

H2S enters the energy transport chain at Level IV, where it binds to the mitochondrial enzyme cytochrome c oxidase.

Recent research on low-level HS toxicity points to increased formation of free radicals and depolarization of the mitochondrial membrane.

This attenuates oxidative phosphorylation and the production of adenosine triphosphate (ATP), resulting in decreased energy.

Given a predisposing genetic background of “hypersusceptibility” or one that compromises DNA repair, H2S may lead to genomic instability or cumulative mutations.
7. Conclusions and Recommendations

There are a sufficient number of intriguing relationships between the symptoms in patients with CFS and what is known about the effects of hydrogen sulfide in the body to warrant a further exploration of my hypothesis. Here are a few suggestions as to where one might begin to explore this concept:

- In general, look first for genetic predisposition, then its potential relationship to environmental insult.

- Check for mitochondrial myopathies and enzyme deficiencies related to iron-sulfur metabolism and the transulfuration pathway, such as CBS (cystathionine beta synthase) and thiosulfate sulfurtransferase, an H2S detoxification enzyme.

- Identify thiol levels in the body.

- Examine environmental factors, such as the relationship between bacteria in the digestive system and bowels and hydrogen sulfide.

- Examine bacteria that either produce or use H2S as a substrate. It may be useful to look closely at bacteria that utilize glutathione to produce hydrogen sulfide.

- Examine exogenous exposures to hydrogen sulfide.

- Examine the relationship between oxygen sensing and hydrogen sulfide, particularly with respect to oxygen tensions.

Acknowledgments:
I wish to express deep gratitude to Carl Peck, who, early in 2007, felt I had made a discovery and guided me through the process of writing a hypothesis. Bruce M. Charlton, editor of the first journal I contacted, offered immediate assistance and patience as I worked to produce a short hypothesis. Suzanne Vernon provided invaluable encouragement and was also instrumental in putting me in touch with Richard Deth, who embraced my research and shared my ideas with many of his colleagues and students.

I wish to acknowledge the inspiration of my daughter, a remarkable young woman who has held fast to her resilient spirit as this extreme disease has laid claim to the everyday joys of a normal, healthy life.

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