

Hypothesis:

Chronic Fatigue Syndrome,
Mitochondrial Hypo-function,
and Hydrogen Sulfide

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Abstract/Summary

Disease conditions evident in Chronic Fatigue Syndrome (CFS) reflect mitochondrial hypo-function, resulting in multi-system hypo-function. Mitochondrial hypo-function can result from disturbances of hydrogen sulfide homeostasis. CFS involves mitochondrial hypo-function related to disturbed hydrogen sulfide homeostasis in the body. Disturbed hydrogen sulfide homeostasis leads to systemic changes at the molecular level. Understanding the role of hydrogen sulfide in the body may provide a unifying lens through which to view the diverse manifestations of this complex disease known as Chronic Fatigue Syndrome.

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Introduction

Defining the debilitating disease known as Chronic Fatigue Syndrome is a challenge. According to the International Association for Chronic Fatigue Syndrome, CFS, (also known as Myalgic Encephalomyelitis, or ME), is an immune-related illness with immune activation or dysfunction resulting from a number of possible root causes, including triggers by infectious agents, environmental sensitivities, genetic factors and/or physical stressors.¹

Many U.S. clinicians treating CFS patients have found the 1994 CDC definition² too ambiguous for diagnostic purposes, preferring to use a more specific case definition, formally adopted by the Canadian government in 2003. Under that definition, a patient with ME/CFS must meet the following criteria for a minimum of six months: unexplained (after excluding known causes) debilitating fatigue, post-exertional malaise and/or fatigue, sleep dysfunction, and pain, and have two or more specific neurological/cognitive manifestations, and one or more symptoms from two of the categories of autonomic, neuroendocrine, and immune disorders.³

A multi-factorial systems approach may provide the greatest opportunity for understanding the complex web of relationships in this disease. I propose that CFS involves an external trigger, possibly infectious and/or environmental, possibly in conjunction with a genetic predisposition, leading to systemic changes at the molecular level. The occurrence of periodic outbreaks is consistent with an external trigger. Understanding the role of hydrogen sulfide in the body may provide a uniform basis in which to view this complex disease.

Data on the interaction of environmental exposures with genetic factors to alter normal biological function are sparse, although this topic recently has become a focus of research at the National Institutes of Health.^{4,5} The systematic integration of diverse data, such as that proposed by the CDC, will certainly broaden our base of knowledge.⁶

Hypothesis *continued*

Mitochondria

The primary manifestation of CFS is a severe and highly debilitating deficit of energy. Energy is generated at the cellular level in the mitochondria, the “power plants” of the body’s oxygen-based aerobic cellular respiration. Adenosine triphosphate (ATP), the molecule the cell uses for the bulk of its energy needs, is produced here. Cells requiring large amounts of ATP, such as muscle cells, have many mitochondria.

Mitochondria are cellular organelles descended from ancient eukaryotes.^{7,8} The eukaryotes had a physiologically diverse range of oxygen requirements, ranging from aerobic, facultatively anaerobic to strictly anaerobic. The study of evolutionary metabolic pathways,^{9,10,11} particularly with respect to substrate flexibility and bacteria/organelle interface, may provide insight into CFS.

Mitochondrial Disease

Mitochondria contain their own DNA (mtDNA). Protein products of this mtDNA join with nuclear DNA-coded proteins in the electron transport chain,¹² where damaged (either through genetic inheritance or through environmental insult) nuclear DNA can result in damage to mtDNA. In addition to defects of mtDNA which can occur as a result of inheritance, damage to DNA can be sustained through environmental injury, e.g., such as that arising from methyl mercury or manganese exposure.^{13,14,15} Thus there are several possible ways in which damage to the mitochondrial DNA can occur.

Mitochondrial disease leads to impaired respiratory chain function and reduced ATP production.¹⁶ Because mitochondria exist in almost all cells of the body, multi-system dysfunction and phenotypic variability are hallmarks of mitochondrial disease. The range of mitochondrial injury and resulting illness is extensive, for example, from severe, irreversible pathogenic early-onset disease such as Leber’s optic neuropathy, which leads to blindness in young adults, to lesser dysfunction associated with metabolic pathways, such as oxidative phosphorylation (OXPHOS) diseases.^{17,18} The understanding of mitochondrial encephalomyopathies is quickly evolving.^{19,20,21}

Hypothesis *continued*

Exogenous Hydrogen Sulfide

H₂S, the gas with a rotten egg odor, is generally considered to be an environmental toxin, on the level of cyanide.^{22,23,24} At a level of 1000 parts per million, breathing H₂S is lethal. In 1999, nearly 130 public health and related groups called for the EPA to list hydrogen sulfide as a hazardous air pollutant. According to their report, demonstrable symptoms of chronic exposure included pronounced deficits in balance and reaction time, as well as such ailments as dizziness, insomnia, and overpowering fatigue, as well as abnormal neurobehavioral functioning and altered mood states (e.g., depression, fatigue, tension, vigor). Further, the report indicated that numerous CNS-brain effects occur including: changes in brain density, headache, memory loss, reduced sense of smell, loss of balance, dizziness, sleep difficulties, and fatigue.²⁵

The traditional explanation of the toxic effects of hydrogen sulfide is based on its property as a chemical asphyxiate; it binds to the mitochondrial enzyme cytochrome c oxidase (iron-containing protein), blocking oxidative phosphorylation and ATP production. In rats, the gas causes an increase of blood lactate concentration and the lactate/pyruvate ratio, leading to anaerobic glycolysis and inhibition of lipid peroxidation.²⁶

Recent research has indicated that exogenous hydrogen sulfide induces functional inhibition and cell death of cytotoxic lymphocyte subsets for CD8 (+) T cells and NK cells.²⁷ Lowered CD8+ T cells and poorly functioning NK cells are among the most robust immunological abnormalities found in CFS.²⁸

Endogenous Hydrogen Sulfide

Within the last decade, interest has been directed towards the role of endogenous H₂S as the “third” gaseous mediator involved in natural biological function, after carbon monoxide and nitric oxide.^{29,30,31,32} Homeostatic abnormalities of the gas in the body have been identified in several disorders, including ulcerative colitis, Alzheimer’s disease,^{33,34} Down’s syndrome³⁵ and possibly in diabetes³⁶ and sudden infant death syndrome.³⁷

Hypothesis *continued*

Of particular interest to the CFS community is that, at certain oxygen tensions, H₂S has been used to produce a (reversible) hibernative state of reduced metabolic activity in mice³⁸, not dissimilar from the disease conditions that exist in patients with Chronic Fatigue Syndrome. Physiological responses induced in the mice included a decrease in core body temperature, an apnea-like sleep state, reduced heart and respiration rates, and severe metabolic changes, with possible vagus nerve involvement. Oxygen consumption dropped by ~50% and carbon dioxide output dropped by ~60% within the first five minutes. By inhibiting cytochrome c oxidase and oxidative phosphorylation, it was theorized that the gas had “**switched off**” the cell’s utilization of oxygen. It recently has been reported that hydrogen sulfide could protect mice in the hibernative state from lethal hypoxia³⁹ and that H₂S serves as an oxygen sensor/transducer, mitigating effects of hypoxia.^{40,41}

Hydrogen Sulfide and Chronic Fatigue Syndrome

The physical responses of hibernation induced by the gas are not unlike the symptoms and torpor experienced by CFS/ME patients. A similar mechanism is postulated to play a role in CFS patients.

H₂S is apparently active in many of the same systems involved in CFS. It is produced from cysteine in the brain by two enzymes, cystathionine beta-synthase and cystathionine gamma lyase, in response to neuronal excitation. There it alters hippocampal long-term potentiation, initiates calcium waves, and regulates the release of corticotrophin-releasing hormone from the hypothalamus.^{42,43} H₂S may also play a role in the control of the neuroendocrine stress axis.^{44,45}

H₂S plays an important role in the cerebrovascular system. It serves as an oxygen sensor/transducer in vertebrate hypoxic vasoconstriction and hypoxic vasodilation.⁴⁶ Low concentrations of H₂S cause arterial vasoconstriction, reverse NO-mediated vasorelaxation and cause an NO-dependent pressor effect in vivo.⁴⁷ It is reported to be a mediator of cerebral ischemic damage.⁴⁸ H₂S is believed to affect vasoactivity in an *oxygen-dependent manner*,⁴⁹ and to regulate the availability of nitric oxide in the vascular system.⁵⁰

Hypothesis *continued*

Genetic evidence of mitochondrial involvement in CFS has been found, including in genes related to fatty acid metabolism, apoptosis, mitochondrial membrane function,⁵¹ protein production in mitochondria,^{52,53} and others.^{54,55} Two studies have found evidence of cytochrome c oxidase gene involvement.⁵⁶ The metabolic processes associated with the production of energy, reactive oxygen species (ROS), otherwise known as free radicals, and the accumulation of mtDNA damage, have been suggested as underlying pathophysiological mechanisms of CFS.^{57,58,59,60}

The mechanisms involving reduction and utilization of oxygen (redox) and those involving ATP, as well as fatty acid metabolism, are all of relevance to mitochondrial processes.

The cell's ability to utilize oxygen in the process of creating ATP is critical. Too much or too little oxygen can be deadly.⁶¹ Mitochondria adapt to hypoxia, or more precisely, to differing oxygen tensions, by altering mitochondrial oxygen consumption.^{62,63,64,65} Further, the role of reactive sulfur species⁶⁶ may be important in the oxidation process and balance of CFS patients. Preferential retention of sulfur amino acids occurs during an inflammatory response, suggesting an increased requirement for cysteine and a higher level of glutathione turnover during sepsis in rats.^{67,68}

H₂S affects the cell's ability to utilize oxygen by inhibiting Level IV of the electron transport chain. The inhibition of mitochondrial complex IV may lead to secondary loss in complex II-III activity, which may lower reactive oxygen species formation.⁶⁹ In addition, hydrogen sulfide binds to hemoglobin in red blood cells, interfering with oxygen transport. Decreased levels of reactive oxygen species can improve cell viability and, in doing so, limit cellular damage induced by homocysteine.⁷⁰ Recent research on the molecular mechanisms of H₂S toxicity points to reactive oxygen species formation and mitochondrial depolarization.⁷¹

Mitochondria show a very high affinity for sulfide that permits its use as an energetic substrate at low micromolar concentrations, hence, below the toxic level. However, if the supply of sulfide exceeds the oxidation rate, poisoning renders mitochondria inefficient and an anaerobic mechanism involving partial reversion of Krebs cycle already known in invertebrates may take place.⁷² Given a predisposing genetic

Hypothesis *continued*

background that compromises DNA repair or “hyper-susceptibility”, H₂S may lead to genomic instability or cumulative mutations.^{73,74,75}

H₂S plays a pivotal role in both aerobic and anaerobic organisms as a signaling mediator.⁷⁶ It contributes significantly to chronic intestinal disorders that are dependent upon gene-environment interactions.^{77,78,79} Impaired butyrate oxidation and raised counts of sulfate-reducing bacteria in the colon of patients with ulcerative colitis indicate that the disease may be induced or aggravated by hydrogen sulfide toxicity.⁸⁰ H₂S induces direct radical-associated DNA damage, highlighting the possible role of sulfide as an environmental insult that, given a predisposing genetic background, may lead to genomic instability or the cumulative mutations characteristic of colorectal cancer.⁸¹

Metal toxicity and glutathione depletion also appear to be affected by H₂S. Both also have also been mentioned as underlying causes of CFS. It is theorized that H₂S can reduce intracellular bound ferric iron to form unbound ferrous iron, which activates iron. Bacteria in the gut produce H₂S, which when combined with ferrous iron, produces insoluble heavy metal sulfides.⁸²

Additionally, H₂S can increase hepatocyte formation of reactive oxygen species. H₂S cytotoxicity also involves a reactive sulfur species, which depletes glutathione (GSH) and activates oxygen to form ROS. Glutathione-depleted hepatocytes have been shown to be susceptible to NaHS cytotoxicity, indicating that GSH detoxifies NaHS (a H₂S source) or H₂S in cells.⁸³ H₂S also plays a role in cellular proliferation and apoptosis.⁸⁴

Recently, gram-negative bacteria, which are increased in gut-intestinal permeability, were implicated in the etiology of CFS⁸⁵, and similarly, in AIDS activation.⁸⁶ The relationship between bacteria, other microorganisms and hydrogen sulfide in the context of chronic fatigue syndrome should be investigated.

Hypothesis *continued*

Conclusion

All of these systems described in the foregoing have a role in CFS. It is proposed that focused research will demonstrate that the mitochondrial hypo-function in CFS can result from abnormalities of hydrogen sulfide homeostasis. Understanding the role of hydrogen sulfide in the body may provide a unifying lens through which to view the diverse manifestations of this complex disease.

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