Chronic fatigue syndrome from vagus nerve infection: A psychoneuroimmunological hypothesis

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Controversies in chronic fatigue syndrome (CFS)

There is a general consensus among CFS researchers that the symptoms seem to reflect an ongoing immune response, perhaps due to viral infection. However, many unresolved questions remain.

Why have so many different pathogens been associated with CFS?

Why is there no one single predictable cause?

Why are cytokine studies so inconsistent?

Why isn't there consistent evidence of active virus in CFS?

Why are women so much more likely to suffer from CFS?

I have proposed a hypothesis that accounts for these questions. The Vagus Nerve Infection Hypothesis (VNIH) of CFS is as follows:

While the sensory vagus nerve normally signals the body to rest when it senses a peripheral infection, that fatigue signal is pathologically exaggerated when an infection is located on the vagus nerve itself.

The innate immune system and sickness behavior

The more evolutionarily ancient division of the immune system launches the same general response when *any* pathogen is detected. Part of this acute phase response is sickness behavior, a brain-based and normally-adaptive involuntary function serving to divert the body's resources toward fighting infection. It includes:

- ✓Fatigue
- ✓Low-grade fever
- ✓Musculoskeletal pain
- ✓Hyperalgesia
- ✓Sleep architecture changes
- ✓ Cognitive impairments
- ✓ Loss of appetite
- ✓ Depression/ malaise
- ✓ Zinc depletion

These are all proinflammatory cytokine-mediated aspects of the innate immune system response to *any* infection. They are also all symptoms of CFS.

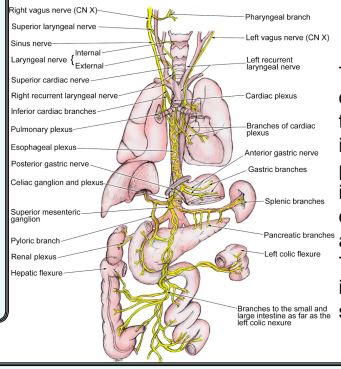
Proinflammatory cytokines signal infection

Proinflammatory cytokines are produced locally when pathogens are detected by innate immune cells such as monocytes, or the glial cells that embed nerve and brain cells. Cytokines such as IL-1β, TNFα, and IL-6 are hydrophilic proteins that do not easily diffuse across the blood-brain barrier to have direct effect upon the brain.

So how does the brain know that the body is sick if cytokines don't access the brain through the bloodstream? Answer: *the vagus nerve*.

interleukin (IL) 1-β

"Given that cytokines are autocrine and paracrine communication factors, their circulating levels have little functional value and represent mostly spillover from the site of cytokine production and action."
– Dantzer et al. (2013). The Neuroimmune Basis of Fatigue



The vagus nerve is a sensitive cytokine detector

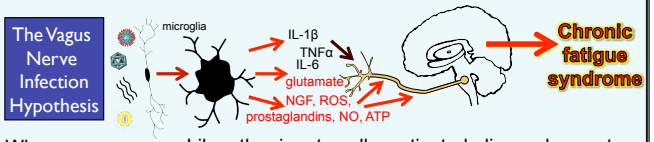
The vagus nerve innervates trunk organs that are especially poised to contact pathogens. When local innate immune cells detect *any* pathogen, they produce pro-inflammatory cytokines, which are detected by chemoreceptors in afferent vagus nerve terminals. The brain receives this signal and initiates normally-adaptive sickness behavior and responses.

Pathogen-activated glial cells exaggerate vagus signaling

When any pathogen contacts any innate immune cell… …the cell releases proinflammatory cytokines locally. The vagus nerve detects those cytokines… …initiating normal sickness responses.

Vagus nerve ganglia and paraganglia are embedded in glia.

Neurotropic pathogens such as HHV-6, enteroviruses, Borrelia burgdorferi (Lyme) & cytomegalovirus are especially likely to contact (para)ganglionic glial cells.



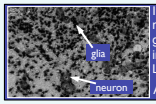
When any pathogen infects a nerve cell, the surrounding glia become activated. Like other innate cells, activated glia produce cytokines, but also produce neuroexcitatory substances. The vagus nerve is not only directly bombarded with cytokines, but the signal is supercharged. Normal sickness responses becomes pathologically strong.

Glial activation adapted from Bilbo & Schwartz (2009); sagittal brain adapted from VanElzakker et al. (2013)

Neuropathic pain & shingles as mechanistic models

The neuropathic pain literature demonstrates that pathogen-induced glial activation can cause pathological nerve signaling. A normal pain signal is enhanced by activated glia, and becomes hyperalgesia or allodynia. The Vagus Nerve Infection Hypothesis (VNIH) posits that normal sickness behavior signaling is enhanced by activated glia to become CFS.

The shingles literature demonstrates that herpesviruses in sensory ganglia continue to cause an ongoing cytokine response, even months into latency.



In-situ hybridization showing TNFα mRNA expression in the satellite glial cells of a trigeminal ganglion infected with latent herpesvirus. Larger cells are sensory neurons.
Adapted from Hukkanen et al. (2002)

Implications: Symptoms

- During exertion, skeletal muscles produce the cytokine/ myokine IL-6, which could explain post-exertional malaise. Deconditioned muscles produce more IL-6.
- Variance in the severity and location of infection along the vagus nerve and in the rest of the body could explain variance in symptom presentation. Neurotropic viruses are known for anterograde movement through nerve tissue.
- The vagus nerve is a structurally and functionally sexually dimorphic organ, which could explain why CFS is much more common in women than in men.

Implications: Treatment options

- According to the VNIH of CFS, possible treatment strategies include glial inhibitors, specific antivirals, vagus nerve stimulation (VNS), and local vagotomy.
- (Para)ganglia are immunoprivileged – meaning protected from antibodies and drugs, similar to the blood-brain barrier.
- Individualized medicine will likely be critical.

References

Bilbo & Schwarz (2009). Early-life programming of later-life brain and behavior: A critical role for the immune system. *Frontiers in Behavioral Neuroscience*. PMID 19738918

Dantzer et al. (2013). The neuroimmune basis of fatigue. *Trends In Neuroscience*. PMID 24239063

HHV-6 image adapted from www.hhv-6foundation.org

Hukkanen et al. (2002). Cytokines in experimental herpes simplex virus infection. *International Reviews of Immunology*. PMID 12486819

Vagus nerve figure: www.cea1.com/anatomy-sistems/anatomy-of-the-vagus-nerve

VanElzakker (2013). Chronic fatigue syndrome from vagus nerve infection: A psychoneuroimmunological hypothesis. *Medical Hypotheses*. PMID 23790471

VanElzakker et al. (2013). From Pavlov to PTSD: The extinction of conditioned fear in rodents, humans, and in anxiety disorders. *Neurobiology of Learning & Memory*. PMID 24321650

Wikipedia.org images of IL-1β, glia, enterovirus, and cytomegalovirus adapted under fair use.