Gulf War illness caused by mitochondrial dysfunction, not inflammation

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Veterans with Gulf War Illness have long struggled to get a proper diagnosis and treatment, despite experiencing symptoms for several decades. Credit: Jakob Owens on Unsplash

Gulf War Illness (GWI) is a chronic multisymptom health condition affecting one-third of all veterans who served in the 1991 Gulf War, most of whom remain afflicted more than 30 years later. Common symptoms include fatigue, headaches, muscle aches, joint pain, diarrhea, insomnia and cognitive impairment.

The condition is believed to have been triggered by veterans' exposure to environmental toxins. However, its exact mechanism in the body continues to be debated, making it difficult to diagnose and treat. The prevailing notion is that inflammation is the driving force of the symptoms, as inflammatory markers are modestly higher in affected veterans than in healthy controls. However, a rival hypothesis suggests mitochondria—the energy-producing organelle found in most cells—may be the true source of the symptoms.

In a new study, researchers at University of California San Diego School of Medicine put both ideas head-to-head, directly assessing mitochondrial impairment and inflammation in 36 individuals, 19 of whom were veterans with GWI. The findings, published July 12, 2023 in *Scientific Reports*, suggest that impaired mitochondrial function, and not inflammation, is the main driver of GWI symptoms and should be the primary target of future clinical interventions.

"This is a radical rethinking of the pathology of GWI," said corresponding author Beatrice Golomb, MD, Ph.D., professor of medicine at UC San Diego School of Medicine. "For veterans who have long struggled to get effective care, this discovery could be a real game changer."

To evaluate the respective roles of mitochondrial function and inflammation in GWI, the researchers acquired muscle biopsies from the study participants and measured the levels of mitochondrial respiratory chain function (MRCF). Inflammation was assessed through participants' blood levels of high-sensitivity C-reactive protein (hsCRP), a common marker of peripheral inflammation.

The researchers then compared this data to the participants' GWI symptoms and found that the severity of symptoms could be predicted by their degree of mitochondrial impairment, but not by their degree of

inflammation. Further statistical analyses found that 17 of the 20 most common GWI symptoms were statistically related to mitochondrial function. In contrast, only one of the 20 symptoms met this criterion for inflammation.

Another set of analyses revealed that the degree to which participants' mitochondria were compromised in converting fat to energy was strongly related to the degree of inflammation in GWI patients, but not in controls. Reduced activity of this process, called fatty acid oxidation, is known to trigger cell death, which then leads to inflammation. Thus the researchers say this suggests that mitochondrial dysfunction may be the reason inflammation is higher in GWI patients.

"Inflammation does appear to be linked to GWI, but our work suggests that it's actually a side effect of the primary issue, which is impaired cell energy," said Golomb.

The researchers also note that many GWI symptoms are expected outcomes of mitochondrial dysfunction. For example, muscles rely heavily on fat to fuel them, so if mitochondrial dysfunction leads to impaired fatty acid oxidation in GWI patients, this could explain the muscle aches and physical fatigue they often experience. Indeed, muscle symptoms in GWI correlated most strongly with the degree of impairment in mitochondrial fatty acid oxidation. Conversely, the brain relies mostly on sugar for energy, and brain symptoms in GWI related most strongly to impairment in mitochondrial energy production using sugar as a fuel.

The findings also have possible implications for other health conditions, including different forms of toxin exposure, aging and even heart disease. Many of these conditions are marked by increased inflammation, yet often do not respond well to anti-inflammatory drugs. Golomb and colleagues argue that mitochondrial impairment may be an

underlying cause for these conditions, creating opportunities for new therapeutic strategies.

"This is the first time that direct evidence for the mitochondrial hypothesis of GWI has been reported," said Golomb. "We hope that it will lead to improved treatment plans for the veterans who have long struggled with this mysterious illness."

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More information: Beatrice A. Golomb et al, Mitochondrial impairment but not peripheral inflammation predicts greater Gulf War illness severity, *Scientific Reports* (2023). DOI: 10.1038/s41598-023-35896-w

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