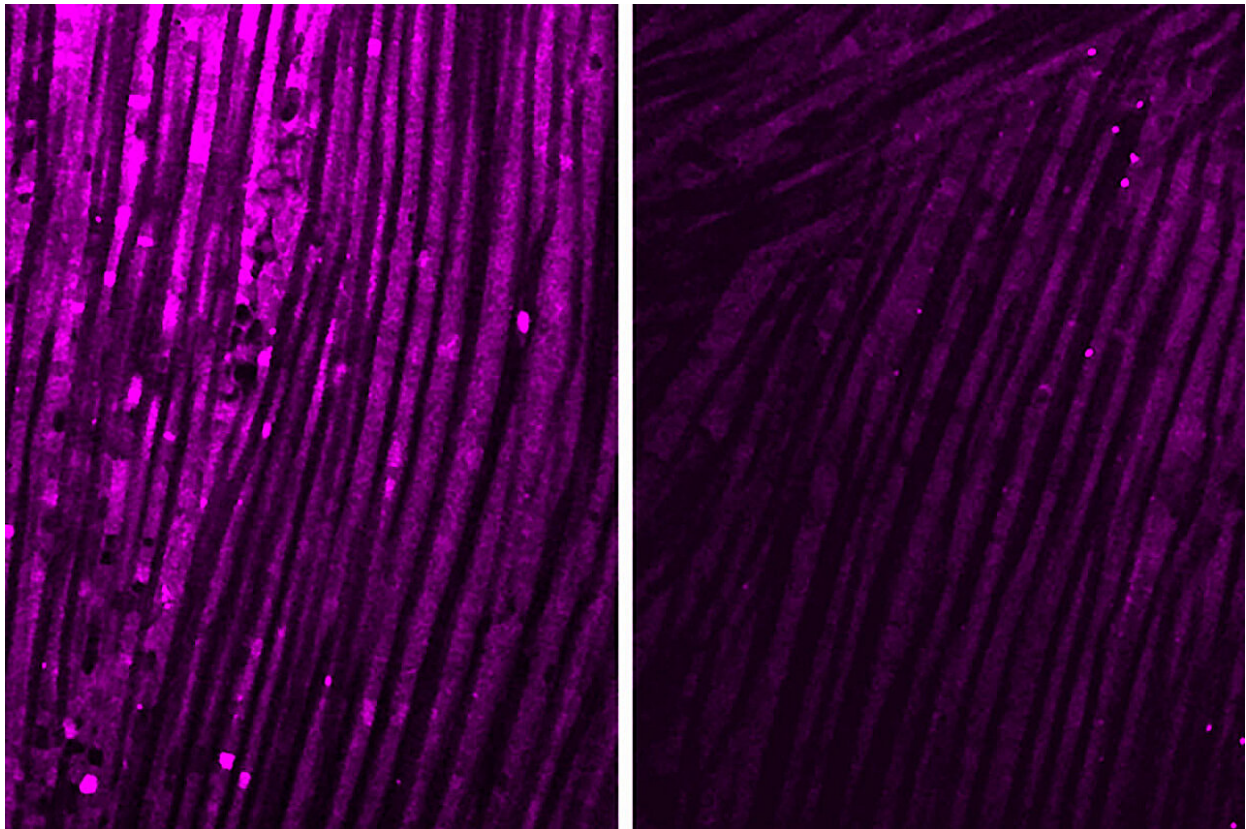


Scientists identify possible way to block muscle fatigue in long COVID, other diseases

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Research from Washington University School of Medicine in St. Louis reveals how brain inflammation triggers extreme muscle weakness across several diseases, including viral infection, bacterial infection and Alzheimer's disease. Shown are fruit fly muscles; the violet staining is a measure of how well mitochondria in muscle cells are producing energy. On the left is a healthy muscle, and on the right is a muscle exposed to IL-6, an immune-related molecule produced by the brain in response to infections or chronic disease. Credit: Shuo Yang

Infections and neurodegenerative diseases cause inflammation in the brain. But for unknown reasons, patients with brain inflammation often develop muscle problems that seem to be independent of the central nervous system. Now, researchers at Washington University School of Medicine in St. Louis have revealed how brain inflammation releases a specific protein that travels from the brain to the muscles and causes a loss of muscle function.

The study, in fruit flies and mice, also identified ways to block this process, which could have implications for treating or preventing the muscle wasting sometimes associated with [inflammatory diseases](#), including bacterial infections, Alzheimer's disease and long COVID.

The study is [published](#) July 12 in the journal *Science Immunology*.

"We are interested in understanding the very deep muscle fatigue that is associated with some common illnesses," said senior author Aaron Johnson, Ph.D., an associate professor of developmental biology.

"Our study suggests that when we get sick, messenger proteins from the brain travel through the bloodstream and reduce energy levels in skeletal muscle. This is more than a lack of motivation to move because we don't feel well. These processes reduce [energy levels](#) in [skeletal muscle](#), decreasing the capacity to move and function normally."

To investigate the effects of brain inflammation on muscle function, the researchers modeled three different types of diseases—an E. coli [bacterial infection](#), a SARS-CoV-2 viral infection and Alzheimer's.

When the brain is exposed to inflammatory proteins characteristic of these diseases, damaging chemicals called [reactive oxygen species](#) build

up. The reactive oxygen species cause [brain cells](#) to produce an immune-related molecule called interleukin-6 (IL-6), which travels throughout the body via the bloodstream.

The researchers found that IL-6 in mice—and the corresponding protein in [fruit flies](#)—reduced energy production in muscles' mitochondria, the energy factories of cells.

"Flies and mice that had COVID-associated proteins in the brain showed reduced motor function—the flies didn't climb as well as they should have, and the mice didn't run as well or as much as control mice," Johnson said.

"We saw similar effects on muscle function when the brain was exposed to bacterial-associated proteins and the Alzheimer's protein amyloid beta. We also see evidence that this effect can become chronic. Even if an infection is cleared quickly, the reduced muscle performance remains many days longer in our experiments."

Johnson, along with collaborators at the University of Florida and first author Shuo Yang, Ph.D.—who did this work as a postdoctoral researcher in Johnson's lab—make the case that the same processes are likely relevant in people.

The bacterial brain infection meningitis is known to increase IL-6 levels and can be associated with muscle issues in some patients, for instance. Among COVID-19 patients, inflammatory SARS-CoV-2 proteins have been found in the brain during autopsy, and many long COVID patients report extreme fatigue and muscle weakness even long after the initial infection has cleared.

Patients with Alzheimer's disease also show increased levels of IL-6 in the blood as well as muscle weakness.

The study pinpoints potential targets for preventing or treating muscle weakness related to [brain inflammation](#). The researchers found that IL-6 activates what is called the JAK-STAT pathway in muscle, and this is what causes the reduced energy production of mitochondria.

Several therapeutics already approved by the Food and Drug Administration for other diseases can block this pathway. JAK inhibitors as well as several monoclonal antibodies against IL-6 are approved to treat various types of arthritis and manage other inflammatory conditions.

"We're not sure why the brain produces a protein signal that is so damaging to muscle function across so many different disease categories," Johnson said.

"If we want to speculate about possible reasons this process has stayed with us over the course of human evolution, despite the damage it does, it could be a way for the brain to reallocate resources to itself as it fights off disease. We need more research to better understand this process and its consequences throughout the body.

"In the meantime, we hope our study encourages more clinical research into this pathway and whether existing treatments that block various parts of it can help the many patients who experience this type of debilitating muscle fatigue," he said.

More information: Shuo Yang et al, Infection and chronic disease activate a systemic brain-muscle signaling axis, *Science Immunology* (2024). [DOI: 10.1126/sciimmunol.adm7908](https://doi.org/10.1126/sciimmunol.adm7908).
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