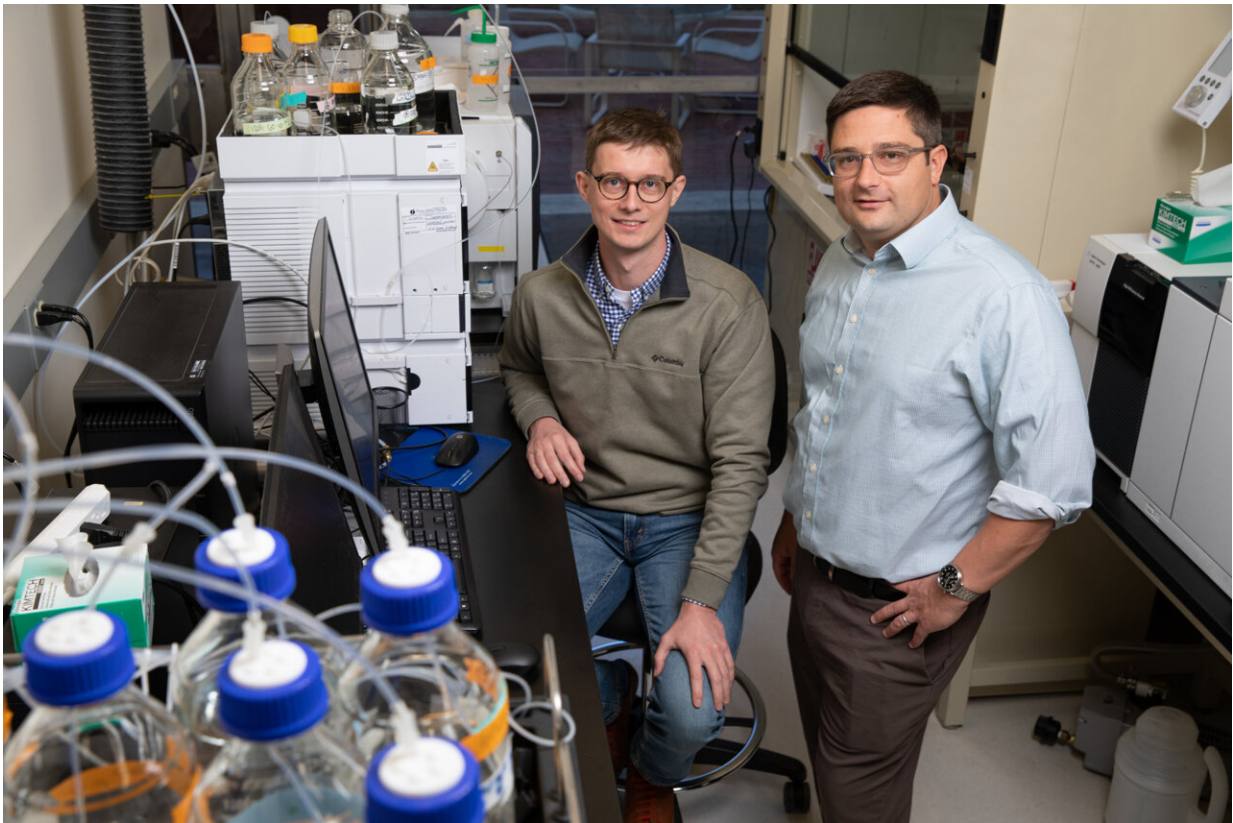


Supplementation with amino acid serine eases neuropathy in diabetic mice

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From left: Michal Handzlik and Christian Metallo. Credit: Salk Institute

Approximately half of people with type 1 or type 2 diabetes experience peripheral neuropathy—weakness, numbness, and pain, primarily in the hands and feet. The condition occurs when high levels of sugar

circulating in the blood damage peripheral nerves. Now, working with mice, Salk Institute researchers have identified another factor contributing to diabetes-associated peripheral neuropathy: altered amino acid metabolism.

The team found that [diabetic mice](#) with low levels of two related amino acids, serine and glycine, are at higher risk for peripheral neuropathy. What's more, the researchers were able to alleviate neuropathy symptoms in diabetic mice by supplementing their diets with serine.

The study, published January 25, 2023 in *Nature*, adds to growing evidence that some often-underappreciated, "non-essential" [amino acids](#) play important roles in the nervous system. The findings may provide a new way to identify people at high risk for peripheral neuropathy, as well as a potential treatment option.

"We were surprised that dialing up and down a non-essential amino acid had such a profound effect on metabolism and diabetic complications," says senior author Christian Metallo, a professor in Salk's Molecular and Cell Biology Laboratory. "It just goes to show that what we think of as dogma can change under different circumstances, such as in disease conditions." Metallo led the study with first author Michal Handzlik, a postdoctoral researcher in his lab.

Amino acids are the building blocks that make up proteins and specialized fat molecules called sphingolipids, which are abundant in the nervous system. Low levels of the amino acid serine force the body to incorporate a different amino acid in sphingolipids, which changes their structure. These atypical sphingolipids then accumulate, which may contribute to peripheral nerve damage. While the team observed this accumulation in diabetic mice, the same amino acid switch and sphingolipid changes occur in a rare human genetic disease marked by peripheral sensory neuropathy, indicating that the phenomenon is

consistent across many species.

To determine whether long-term, chronic serine deficiency drives peripheral neuropathy, Metallo's team fed mice either control or serine-free diets in combination with either low-fat or high-fat diets for up to 12 months. The researchers were surprised to find that low serine, in combination with a high-fat diet, accelerated the onset of peripheral neuropathy in the mice. In contrast, serine supplementation in diabetic mice slowed the progression of peripheral neuropathy, and the mice fared better.

The researchers also tested the compound myriocin, which inhibits the enzyme that switches out serine for another amino acid as sphingolipids are assembled. Myriocin treatment reduced peripheral neuropathy symptoms in mice fed a high-fat, serine-free diet. These findings underscore the importance of amino acid metabolism and sphingolipid production in the maintenance of a healthy peripheral nervous system.

Serine deficiency has also been associated with various neurodegenerative disorders. For example, Metallo and collaborators previously found a link between altered serine and sphingolipid metabolism in patients with macular telangiectasia type 2, a condition that causes vision loss. In [mice](#), reduced serine led to increased levels of atypical retinal sphingolipids and reduced vision. Serine is currently being tested in clinical trials for its safety and efficacy in treating macular telangiectasia and Alzheimer's disease.

Peripheral neuropathy is typically managed with dietary changes to reduce blood sugar levels, as well as pain relievers, physical therapy, and mobility aids, such as canes and wheelchairs. Foods naturally rich in serine include soybeans, nuts, eggs, chickpeas, lentils, meat, and fish, and serine supplements are inexpensive and available over the counter.

Yet the researchers say it's premature to advise people with diabetes to take serine supplements to prevent [neuropathy](#).

"You would likely need to take a lot to make a difference, and not everyone needs extra serine," Metallo says. "We need more time to understand serine physiology in humans and explore potential downsides to supplementation."

To this end, Metallo and Handzlik are now developing a serine tolerance test, similar to a glucose tolerance test used to diagnose diabetes.

"We want to identify those at highest risk for [peripheral neuropathy](#) so we can treat only those who might benefit most," says Handzlik.

More information: Christian Metallo, Insulin-regulated serine and lipid metabolism drive peripheral neuropathy, *Nature* (2023). [DOI: 10.1038/s41586-022-05637-6](#).
www.nature.com/articles/s41586-022-05637-6

Provided by Salk Institute

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