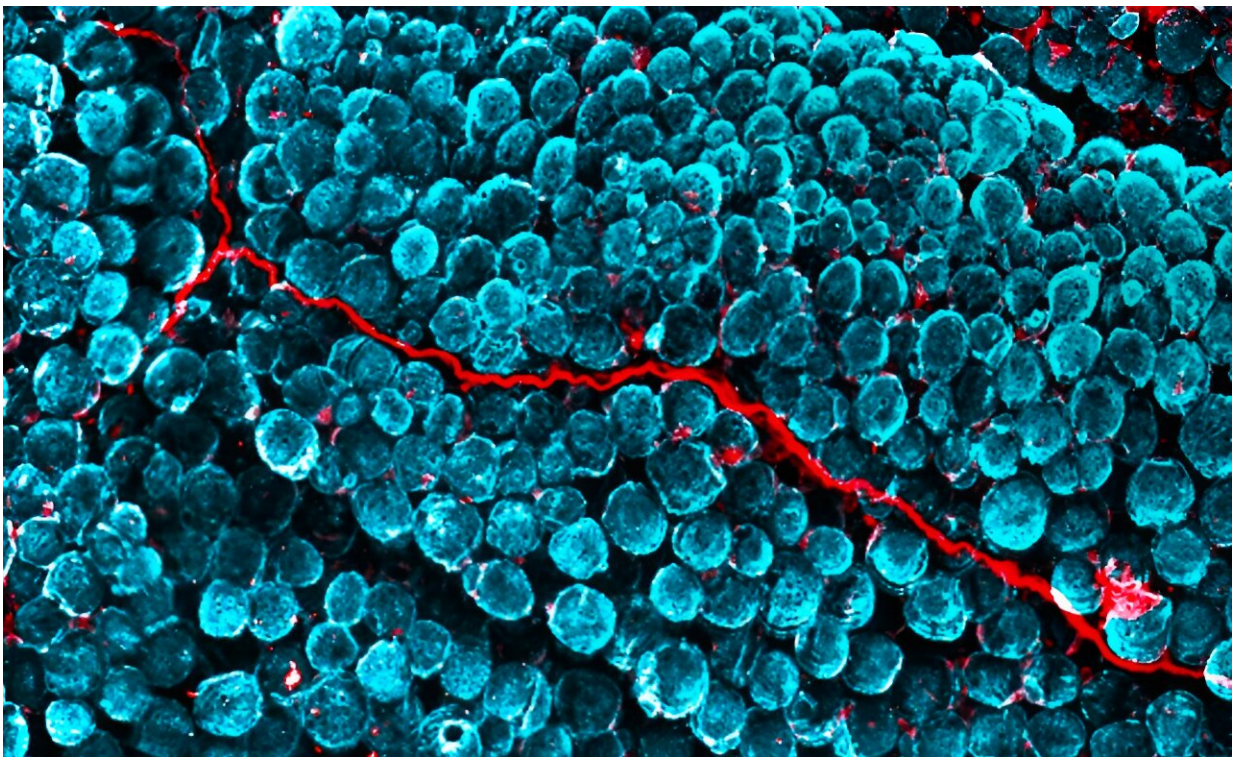


After spinal cord injury, neurons wreak havoc on metabolism: Study finds common drug may prevent some of the effects

April 24 2024, by Emily Caldwell



Fluorescence image of sensory axons, in red, connecting with visceral white fat tissue seven days after a spinal cord injury in an adult mouse. Credit: Andrea Tedeschi

Conditions such as diabetes, heart attack, and vascular diseases

commonly diagnosed in people with spinal cord injuries can be traced to abnormal post-injury neuronal activity that causes abdominal fat tissue compounds to leak and pool in the liver and other organs, a new animal study has found.

After discovering the connection between dysregulated neuron function and the breakdown of triglycerides in fat tissue in mice, researchers found that a short course of the drug gabapentin, commonly prescribed for nerve pain, prevented the damaging metabolic effects of spinal cord injury.

Gabapentin inhibits a neural protein that, after the nervous system is damaged, becomes overactive and causes communication problems—in this case, affecting sensory neurons and the abdominal fat tissue to which they're sending signals.

"We believe there is a maladaptive reorganization of the sensory system that causes the fat to undergo changes, initiating a chain of reactions—triglycerides start breaking down into glycerol and free fatty acids that are released in circulation and taken up by the liver, the heart, the muscles, and accumulating, setting up conditions for [insulin resistance](#)," said senior author Andrea Tedeschi, assistant professor of neuroscience in The Ohio State University College of Medicine.

"Through administration of gabapentin, we were able to normalize metabolic function."

The study is published in [Cell Reports Medicine](#).

Previous research has found that cardiometabolic diseases are among the leading causes of death in people who have experienced a spinal cord injury. These often chronic disorders can be related to dysfunction in visceral white fat (or adipose tissue), which has a complex metabolic

role of storing energy and releasing fatty acids as needed for fuel, but also helping keep blood sugar levels at an even keel.

Earlier investigations of these diseases in people with neuronal damage have focused on adipose tissue function and the role of the sympathetic nervous system—nerve activity known for its "fight or flight" response, but also a regulator of adipose tissue that surrounds the abdominal organs.

Instead, Debasish Roy—a postdoctoral researcher in the Tedeschi lab and the first author of the paper—decided to focus on sensory neurons in this context. Tedeschi and colleagues have previously shown that a neuronal receptor protein called alpha2delta1 is overexpressed after spinal cord injury, and its increased activation interferes with the post-injury function of axons, the long, slender extensions of nerve cell bodies that transmit messages.

In this new work, researchers first observed how sensory neurons connect to [adipose tissue](#) under healthy conditions and created a spinal cord injury mouse model that affected only those neurons—without interrupting the sympathetic nervous system.

Experiments revealed a cascade of abnormal activity within seven days after the injury in neurons—though only in their communication function, not their regrowth or structure—and in visceral fat tissue. Expression of the alpha2delta1 receptor in [sensory neurons](#) increased as they over-secreted a neuropeptide called CGRP, all while communicating through synaptic transmission to the fat tissue—which, in a state of dysregulation, drove up levels of a receptor protein that engaged with the CGRP.

"These are quite rapid changes. As soon as we disrupt sensory processing as a result of spinal cord injury, we see changes in the fat," Tedeschi

said. "A vicious cycle is established—it's almost like you're pressing the gas pedal so your car can run out of gas but someone else continues to refill the tank, so it never runs out."

The result is the spillover of free fatty acids and glycerol from fat tissue, a process called lipolysis, that has gone out of control. Results also showed an increase in blood flow in fat tissue and recruitment of immune cells to the environment.

"The fat is responding to the presence of CGRP, and it's activating lipolysis," Tedeschi said. "CGRP is also a potent vasodilator, and we saw increased vascularization of the fat—[new blood vessels](#) forming as a result of the spinal cord injury. And the recruitment of monocytes can help set up a chronic pro-inflammatory state."

Silencing the genes that encode the alpha2delta1 receptor restored the fat tissue to normal function, indicating that gabapentin—which targets alpha2delta1 and its partner, alpha2delta2—was a good treatment candidate. Tedeschi's lab has previously shown in animal studies that gabapentin helped restore limb function after spinal cord injury and boosted functional recovery after stroke.

But in these experiments, Roy discovered something tricky about gabapentin: The drug prevented changes in abdominal fat tissue and lowered CGRP in the blood—and in turn prevented spillover of fatty acids into the liver a month later, establishing normal metabolic conditions. But paradoxically, the mice developed insulin resistance—a known side effect of gabapentin.

The team changed drug delivery tactics, starting with a high dose and tapering off—and stopping after four weeks.

"This way, we were able to normalize metabolism to a condition much

more similar to control mice," Roy said. "This suggests that as we discontinue administration of the drug, we retain beneficial action and prevent spillover of lipids in the liver. That was really exciting."

Finally, researchers examined how genes known to regulate white fat tissue were affected by targeting $\alpha 2\delta 1$ genetically or with gabapentin, and found both of these interventions after spinal cord injury suppress genes responsible for disrupting metabolic functions.

Tedeschi said the combined findings suggest starting gabapentin treatment early after a spinal cord injury may protect against detrimental conditions involving fat tissue that lead to cardiometabolic disease—and could enable discontinuing the drug while retaining its benefits and lowering the risk for side effects.

More information: Debasish Roy et al, $\alpha 2\delta 1$ -mediated maladaptive sensory plasticity disrupts adipose tissue homeostasis following spinal cord injury, *Cell Reports Medicine* (2024). [DOI: 10.1016/j.xcrm.2024.101525](https://doi.org/10.1016/j.xcrm.2024.101525)

Provided by The Ohio State University

Citation: After spinal cord injury, neurons wreak havoc on metabolism: Study finds common drug may prevent some of the effects (2024, April 24) retrieved 6 May 2024 from <https://medicalxpress.com/news/2024-04-spinal-cord-injury-neurons-wreak.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.