

What wintering squirrels can teach astronauts

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Thirteen-lined ground squirrels curled up for seasonal hibernation can slow their metabolic rates to as little as 1 percent of their waking activity. Credit: Photo courtesy Rob Streiffer

When bears and ground squirrels hibernate in winter, they stop eating, lasting until spring simply on the fat reserves they've stored up in their bodies. Usually, this sort of prolonged fasting and inactivity would significantly reduce the mass and function of muscle, but hibernators don't suffer this fate. How they avoid it, however, has been a mystery.

Now, in research published in *Science*, an Université de Montréal biologist has figured out why, and his findings could have implications for, of all things, the future of space travel . By studying a variety called the 13-lined ground squirrel that is common in North America, Matthew Regan has confirmed a theory known as "urea nitrogen salvage" dating back to the 1980s.

The theory posits that hibernators harness a metabolic trick of their gut microbes to recycle the nitrogen present in urea, a waste compound that is usually excreted as urine, and use it to build new tissue proteins.

How could this discovery be of use in space? Theoretically, Regan posits, by helping astronauts minimize their own muscle-loss problems caused by microgravity-induced suppression of protein synthesis and which they now try to reduce by intensively exercising.

If a way could be found to augment the astronauts' muscle protein synthesis processes using urea nitrogen salvage, they could be able to achieve better muscle health during long voyages into deep space in spacecraft too small for the usual exercise equipment, the argument goes.

"Because we know which muscle proteins are suppressed during spaceflight, we can compare these proteins with those that are enhanced by urea nitrogen salvage during hibernation," said Regan, who carried

out this research while a postdoc at the University of Wisconsin-Madison.

He is now continuing his work through a Canadian Space Agency research grant at UdeM, where he last year took up a position as assistant professor of animal physiology in the Department of Biological Sciences.

"If," Regan continued, "there is an overlap between the proteins in spaceflight and the ones from hibernation, then it suggests this process may have benefits to muscle health during spaceflight."

A model hibernator

In his study, Regan designed a series of techniques and experiments to investigate the major steps in the urea salvage process and provide evidence for whether or not they occur in the 13-lined ground squirrel when it hibernates.

To do that, in their lab they injected their test squirrels' blood with "double-labeled" urea, meaning the urea's carbon atom was ^{13}C instead of the usual ^{12}C , and its [nitrogen atoms](#) were ^{15}N instead of the usual ^{14}N . These labels allowed them to track the urea-sourced carbon and nitrogen through the different steps of the urea nitrogen salvage process.

That process, they found, led from the initial transport of urea from the blood into the gut, to the breakdown of urea into its component parts by gut microbes, to the flow of substances—called metabolites—containing urea nitrogen back into the animal, and finally to the eventual appearance of this urea nitrogen in tissue protein.

"Essentially, seeing ^{13}C and/or ^{15}N in metabolites at these various steps indicated that they originated from urea, and thus, that the hibernator

was using urea nitrogen salvage," said Regan.

He did his experiments on squirrels with and without gut microbiomes at three times of the year: summer, when they were active and not hibernating; early winter, when they were one month into fasting and hibernation; and late winter, when they were four months into fasting and hibernation.

'Clear evidence of nitrogen salvage'

What they found was definitive: at each step of the process, there was clear evidence of urea nitrogen salvage by the squirrels with intact gut microbiomes.

Importantly, the squirrels with depleted gut microbiomes displayed no evidence of urea nitrogen salvage at any step, confirming this process was wholly dependent on the gut microbes' ability to degrade urea, something the squirrels themselves cannot do.

Regan and his team also made two other important findings:

- First, the incorporation of urea nitrogen into the tissue protein of the squirrels was highest during late winter, suggesting that urea nitrogen salvage becomes more active as the hibernation season proceeds. This is unlike most physiological processes during hibernation, when tend to be significantly reduced.
- Second, there was evidence the microbes themselves were using the urea nitrogen to build their own new proteins, which is useful for them because they, like the squirrel, are under conditions of fasting hibernation. Thus, both the squirrel and its microbes benefit from urea nitrogen salvage, which makes this process a true symbiosis.

What this means, Regan said, is that the squirrels emerge from hibernation in the spring in good shape. This is important because the year's only mating season, which is a time of intense physical activity for both males and females, occurs directly after they emerge from hibernation. Tissue function—particularly muscle tissue function—is therefore highly important for a successful mating season.

"By facilitating muscle protein synthesis late in the hibernation season, urea nitrogen salvage may help optimize the emerging squirrels' muscle function and contribute to their reproductive success during the mating season," said Regan. "Urea nitrogen salvage may therefore enhance the animals' overall biological fitness."

Starving masses and the elderly

Beyond the implications for space travel and the health of astronauts, Regan's discovery could have more immediate impacts now right here on Earth—in the starving masses of the underdeveloped world, and in the elderly.

Hundreds of millions of people globally experience muscle wasting as a consequence of various conditions—undernourishment, for instance, affects over 805 million people globally. More prevalent in Canada is sarcopenia, an age-related decline in muscle mass stemming from anabolic insensitivity that affects all humans, leading to a 30- to 50-percent decline in skeletal muscle mass between the ages 40 and 80.

"The mechanisms that mammals like the 13-lined ground [squirrel](#) have naturally evolved to maintain protein balance in their own nitrogen-limited situations may inform strategies for maximizing the health of other nitrogen-limited animals, including humans," said Regan. One solution might be to develop a pre- or probiotic pill that people could take to promote a gut microbiome of the kind that hibernators like

squirrels have.

"To be clear, these applications, though theoretically possible, are a long way from delivery, and a lot of additional work is needed to translate this naturally evolved mechanism safely and effectively to humans," Regan said.

"But one thing I find encouraging is that [a study](#) from the early 1990s provided some evidence that humans are capable of recycling small amounts of [urea nitrogen](#) via this same process. This suggests that the necessary machinery is in place. It just needs to be optimized."

More information: Matthew D. Regan et al, Urea nitrogen recycling via gut symbionts increases in hibernating ground squirrels over the winter, *Science* (2022). [DOI: 10.1126/science.abh2950](https://doi.org/10.1126/science.abh2950).
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