Learning from the bears

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Credit: Max Delbrück Center for Molecular Medicine

Grizzly bears spend many months in hibernation, but their muscles do not suffer from the lack of movement. In the journal *Scientific Reports*, a team led by Michael Gotthardt reports on how they manage to do this. The grizzly bears' strategy could help prevent muscle atrophy in humans as well.

A grizzly bear only knows three seasons during the year. Its time of activity starts between March and May. Around September the bear

begins to eat large quantities of food. And sometime between November and January, it falls into hibernation. From a physiological point of view, this is the strangest time of all. The bear's metabolism and heart rate drop rapidly. It excretes neither urine nor feces. The amount of nitrogen in the blood increases drastically and the bear becomes resistant to the hormone insulin.

A person could hardly survive this four-month phase in a healthy state. Afterwards, he or she would most likely have to cope with thromboses or psychological changes. Above all, the muscles would suffer from this prolonged period of disuse. Anyone who has ever had an arm or leg in a cast for a few weeks or has had to lie in bed for a long time due to an illness has probably experienced this.

A little sluggish, but otherwise fine

Not so the grizzly bear. In the spring, the bear wakes up from hibernation, perhaps still a bit sluggish at first, but otherwise well. Many scientists have long been interested in the bear's strategies for adapting to its three seasons.

A team led by Professor Michael Gotthardt, head of the Neuromuscular and Cardiovascular Cell Biology group at the Max Delbrueck Center for Molecular Medicine (MDC) in Berlin, has now investigated how the bear's muscles manage to survive hibernation virtually unharmed. The scientists from Berlin, Greifswald and the United States were particularly interested in the question of which genes in the bear's muscle cells are transcribed and converted into proteins, and what effect this has on the cells.

Understanding and copying the tricks of nature

"Muscle atrophy is a real human problem that occurs in many circumstances. We are still not very good at preventing it," says the lead author of the study, Dr. Douaa Mugahid, once a member of Gotthardt's research group and now a postdoctoral researcher in the laboratory of Professor Marc Kirschner of the Department of Systems Biology at Harvard Medical School in Boston.

"For me, the beauty of our work was to learn how nature has perfected a way to maintain muscle functions under the difficult conditions of hibernation," says Mugahid. "If we can better understand these strategies, we will be able to develop novel and non-intuitive methods to better prevent and treat muscle atrophy in patients."

Gene sequencing and mass spectrometry

To understand the bears' tricks, the team led by Mugahid and Gotthardt examined muscle samples from grizzly bears both during and between the times of hibernation, which they had received from Washington State University. "By combining cutting-edge sequencing techniques with mass spectrometry, we wanted to determine which genes and proteins are upregulated or shut down both during and between the times of hibernation," explains Gotthardt.

"This task proved to be tricky—because neither the full genome nor the proteome, i.e., the totality of all proteins of the grizzly bear, were known," says the MDC scientist. In a further step, he and his team compared the findings with observations of humans, mice and nematode worms.

Non-essential amino acids allowed muscle cells to grow

As the researchers reported in the journal *Scientific Reports*, they found proteins in their experiments that strongly influence a bear's amino acid metabolism during hibernation. As a result, its muscle cells contain higher amounts of certain non-essential amino acids (NEAAs).

"In experiments with isolated muscle cells of humans and mice that exhibit muscle atrophy, cell growth could also be stimulated by NEAAs," says Gotthardt, adding that "it is known, however, from earlier clinical studies that the administration of amino acids in the form of pills or powders is not enough to prevent muscle atrophy in elderly or bedridden people."

"Obviously, it is important for the muscle to produce these amino acids itself—otherwise the amino acids might not reach the places where they are needed," speculates the MDC scientist. A therapeutic starting point, he says, could be the attempt to induce the human muscle to produce NEAAs itself by activating corresponding metabolic pathways with suitable agents during longer rest periods.

Tissue samples from bedridden patients

In order to find out which signaling pathways need to be activated in the muscle, Gotthardt and his team compared the activity of genes in grizzly bears, humans and mice. The required data came from elderly or bedridden patients and from mice suffering from muscle atrophy—for example, as a result of reduced movement after the application of a plaster cast. "We wanted to find out which genes are regulated differently between animals that hibernate and those that do not," explains Gotthardt.

However, the scientists came across a whole series of such genes. To narrow down the possible candidates that could prove to be a starting point for muscle atrophy therapy, the team subsequently carried out

experiments with nematode worms. "In worms, individual genes can be deactivated relatively easily and one can quickly see what effects this has on muscle growth," explains Gotthardt.

A gene for circadian rhythms

With the help of these experiments, his team has now found a handful of genes whose influence they hope to further investigate in future experiments with mice. These include the genes Pdk4 and Serpinf1, which are involved in glucose and amino acid metabolism, and the gene Rora, which contributes to the development of circadian rhythms. "We will now examine the effects of deactivating these genes," says Gotthardt. "After all, they are only suitable as therapeutic targets if there are either limited side effects or none at all."

More information: D. A. Mugahid et al, Proteomic and Transcriptomic Changes in Hibernating Grizzly Bears Reveal Metabolic and Signaling Pathways that Protect against Muscle Atrophy, *Scientific Reports* (2019). DOI: 10.1038/s41598-019-56007-8

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