NATURE | NEWS

Plump grizzlies offer diabetes clue

Selective gene expression in stout bears helps them to maintain steady blood sugar.

Heidi Ledford

05 August 2014

As summer fades to autumn each year, grizzly bears embark on a wild, gluttonous feast. By the time they settle down for their long winter snooze, they have plenty of fat stores to last through the cold.

Yet despite this annual descent into obesity, researchers have found that the bears don't succumb to metabolic ailments — like poor blood sugar control — commonly found in obese humans[1]. By studying how bears pull off this ponderous feat, scientists hope to find new ways to tackle diabetes in humans.

Bears make for large and unruly study subjects, concedes Kevin Corbit, who studies metabolic diseases at Amgen, a biotechnology company in Thousand Oaks, California. But rodents have proved to be poor models for human disease, he adds, and in bears, evolution has already designed the crucial experiments. "I believe there is an animal out there that has the answer to any human ailment," he says. "We just have to go and find it."

To find an answer to diabetes, Corbit teamed up with bear specialists in Washington to study grizzly bears (*Ursos arctos horribilis*) that had been removed from Yellowstone National Park for being a nuisance to humans. The bears were housed in a 0.8-hectare abandoned primate research colony by the Snake River in Washington.

Insulin challenge

Corbit and his colleagues measured the bears' blood sugar levels at three different times of year: in October, during the pre-hibernation gluttony; in January, while the animals were hibernating; and in May, when they woke up. The team found that the bears' blood sugar levels remained remarkably stable, as did their concentrations of insulin, a hormone that prompts cells to take up sugar from the blood.

Obese humans often become resistant to insulin, leading blood sugar levels to spike. To find out whether the same process occurs in bears, Corbit and his colleagues injected the animals with insulin at each study interval, and tracked their response.

The most striking response occurred when the bears were injected with insulin during the crucial period of feeding before hibernation, when the animals most resembled obese humans. Insulin doses similar to those used by humans nearly killed the animals, and the researchers realized that the bears were not responding to their newfound corpulence by becoming insulin resistant, as a human might. Instead, something was boosting the bears' insulin sensitivity. "I said, 'My god, I think we've stumbled onto something pretty amazing,'" says Corbit.

Pertinent protein

The team then found that expression of PTEN, a protein that regulates cell growth and division, was reduced in the obese bears' fat, but not in other tissues that were tested, the team reports today in *Cell Metabolism*[1]. PTEN was linked to diabetes two years ago, when Anna Gloyn, a diabetes researcher at the University of Oxford, UK, and her colleagues reported that humans who lack a copy of the *PTEN* gene tend to be obese but metabolically healthy[2].

That discovery raised the tantalizing possibility of combating diabetes by blocking PTEN, says Gloyn. But there was a key problem: study participants who lacked a copy of the *PTEN* gene were also prone to cancer.

The bear studies could reveal a way around this problem, she says, because the bears have evolved a way to shut down PTEN specifically in fat, without affecting expression in other tissues. Corbit and his team hope to find out how the bears do this, and whether it can yield a new target in the fight against diabetes.

Gloyn says the studies in bears could be very enlightening, though she doesn't plan to switch her own work to bears any time soon. "I have an enormous amount of respect for working with that model organism," says Gloyn. "But I'm glad I didn't have to take those

biopsies.”

Nature | doi:10.1038/nature.2014.15665

References

1. Nelson, O. L., *et al*. *Cell Metab*. **20**, 376–382 (2014).
2. Pal, A., *et al*. *New Engl. J. Med*. **367**, 1002–1011 (2012).