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Advanced

PAPER 3: General and Practical Applications in Biology

Scientific article for use with Question 8

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Scientific article for use with Question 8

THE BIG SLEEP

Were human ancestors able to hibernate and what could that mean for our health, asks Alex Wilkins.

1. IF YOU could rewind the evolutionary clock millions of years, you might discover that your ancestors had a remarkable trait. It wouldn't be obvious at first. But in certain conditions – if food were scarce or there were a cold snap – it is possible that their eyes would grow heavy and their bodies begin to slow until, eventually, they switched off entirely. They would be hibernating.

2. In this low-energy state, today's hibernators can fend off a remarkable array of threats, from the inside and out. Extreme cold and famine are the obvious ones, but hibernation also has the power to combat conditions that plague modern humans, including Alzheimer's disease, stroke and heart attack. It could even hold the key to longevity and colonising space. No wonder some researchers are keen to reinstate what might have been our long-lost superpower.

3. The idea that ancient humans could hibernate may seem farfetched, but mounting evidence suggests that many non-hibernating mammals retain an ability to enter reduced-energy states, including through dormant brain-signalling pathways that slow metabolism. "The distribution of hibernating species on the tree of mammals makes the likely conclusion that the common ancestor of all mammals was a hibernator," says Sandy Martin at the University of Colorado. "It's possible we all have the genetic hardware."

4. It remains to be seen whether any underlying circuitry can be fired up enough to bestow us with some of hibernation's protective properties. But the potential spoils are too great not to try.

5. Hibernation is often associated with small mammals, such as dormice, hedgehogs and bats, but it is also common among reptiles, amphibians and even insects. It resists easy definition, though. In German, Turkish and many other languages, hibernation translates literally to "winter sleep" – and it does bear a passing resemblance to this. But comparing hibernation to sleep is like comparing apples to oranges, according to Vladyslav Vyazovskiy at the University of Oxford, who studies both. "There are criteria for defining sleep and they are purely brain-centric, but hibernation is defined based on metabolism," he says. "This means that, technically, you can be awake and hibernating or asleep and hibernating."

6. In essence, hibernation centres on a state called torpor, in which an animal decreases its physiological activity, marked by a reduction in body temperature and metabolism. The length and extremity of these changes varies hugely. The drop in body temperature can be severe and last for weeks or brief and entail a decrease of only a few degrees. The accompanying metabolic reduction can be near total or only 10 to 20 per cent. What's more, some hibernators regularly come in and out of torpor into states of arousal, while others stay metabolically suppressed.

7. "Among hibernating mammals, there's a continuum of hibernation," says Matthew Regan at the University of Montreal, Canada. At one end, there is the thirteen-lined ground squirrel (*Ictidomys tridecemlineatus*), one of the most studied hibernators, which lowers its body temperature in successive cycles of torpor and arousal until it is barely above the temperature of its environment. It can stay in this state without food or water for more than six months, suspending many bodily functions and recycling key nutrients through specially adapted processes.

8. At the other end of the continuum are large species such as bears. The black bear (*Ursus americanus*), for example, lowers its core temperature by no more than about 6 °C and reduces its metabolic requirements by a quarter – a significant saving for such a modest temperature decrease. "Bears highlight other means of metabolic suppression that are independent of core temperature. And those mechanisms are really very poorly understood," says Kelly Drew at the University of Alaska in Fairbanks.

9. Most experts believe that if we are ever to enter a state of synthetic torpor, it will be similar to that of a less-extreme hibernator. "It's not feasible to think that humans could get down to the levels of the small hibernators, but you can get an awful lot of value from the shallow metabolic depression of a bear," says Hannah Carey at the University of Wisconsin. In particular, it could be extremely useful for long-distance space travel (see "To blearily go").

10. To begin with, we need to understand the weird processes that happen within the bodies of hibernators. Progress here has been rapid in recent years, not least when it comes to identifying the genes involved. Martin is a pioneer. For decades, she has collected and frozen tissue samples taken from a wide range of mammals over the course of their hibernation. "The idea is that the tissue bank is carefully timed, so that you get good information about levels of gene products, which change across a torpor bout, or change very rapidly during the rewarming period, and change seasonally," she says.

11. Martin's grand vision was to analyse these timed tissue samples to identify the genes that throw the switches controlling hibernation in mammals. Once located, these genes could be studied and possibly modified to mimic the beneficial properties that hibernation bestows. When Martin started her tissue bank, a dearth of technology and resources made this extremely challenging. It was difficult to look at more than one gene at a time or find which genes were being expressed across the whole organism. But now things are different. "The tools are finally catching up to the ability to actually use [the samples] in a way that will be productive," she says. Progress has been particularly strong in an area of research called comparative genomics, which compares the complete genomes of different species to identify important genes.

The Arctic ground squirrel can lower its body temperature to −2.9 °C during torpor

(Source: © Nature Picture Library/Alamy Stock Photo)

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12. Martin retired from active research this year, but she has passed on her treasure trove to one of her ex-students, Katharine Grabek, who co-founded a California-based comparative genomics start-up called Fauna Bio. Grabek and her team are using findings from the tissue bank, along with a raft of other information, such as transcriptomes – descriptions of the different ways genes make proteins – and human gene data, to identify targets for drugs that can replicate hibernation's benefits.

Genomic insights

13. For instance, the thirteen-lined ground squirrel recycles its urea to preserve nutrients, cleans out harmful brain plaques commonly associated with Alzheimer's in humans, mitigates the insulin sensitivity that comes with huge weight gain before winter and appears to experience no ill consequences from severe spikes and troughs in blood pressure as it comes out of hibernation. By comparing its genome with those from more than 50 other hibernating and non-hibernating mammals, Grabek and her team have already identified molecules that appear to protect against high blood pressure, coronary heart disease and heart infections.

14. As they expand their sample collections and analysis, they hope to identify molecules associated with other conditions that affect human health, and eventually use these findings to design therapeutic drugs.

To blearily go

A As the study of hibernation progresses, it has come to the attention of space agencies looking to protect astronauts on long missions. "We have a real interest in understanding this better because it will solve some of our issues, in a very elegant way that otherwise would require developing new propulsion systems to shorten trip durations," says Leopold Summerer at the European Space Agency (ESA), who leads a team that looks at innovative space travel solutions, like hibernation.

B If ESA, NASA or SpaceX is to put people on Mars, then astronauts will have to spend months on a tiny spaceship with minimal food, in microgravity where their bones and muscles will waste away, being bombarded by cosmic radiation in the absence of Earth's magnetic field. Helpfully, these resemble many of the conditions hibernators appear able to survive: bears and squirrels can preserve bone structure while in torpor, the state accompanying hibernation in which metabolic rate is reduced. Squirrels have also shown resistance to high levels of radiation while hibernating. And Summerer's team is now testing how the cells of hibernators perform in microgravity to see whether torpor might be a viable spaceflight strategy.

C NASA is also funding research in this area and consulting hibernation scientists. One company it is collaborating with is Spaceworks. Its chief executive, John Bradford, says the firm's aim is to lower body temperature from 37.5 °C to around 32 °C, which would cut metabolic activity by about 50 per cent. A flight to Mars would take four to six months, he says. "We don't think you could put people in this state for the entire duration. We were envisioning the crew would cycle through these two-week stints of kind of extended sleep periods, and they'd be active for a couple of days, and then go back into stasis again."

15. Other potential payoffs for medicine are coming from research that aims to understand the changes happening within the brains of hibernators. Much of the focus has been on a neurotransmitter called adenosine, which, among other things, is linked with sleep: when adenosine binds to receptors in the brain's hippocampus, neural activity slows and you feel sleepy. In 2011, when Drew and her colleagues gave Arctic ground squirrels (*Urocitellus parryii*) drugs that either activate or suppress these adenosine pathways, the squirrels spontaneously entered and exited states of torpor. But there was a catch: this only worked in winter when the squirrels were already primed for hibernating. Why that might be remains a mystery. Still, it left Drew and her team wondering what effect adenosine might have in mammals that don't hibernate.

16. To find out, they have since done similar experiments with rats. These didn't result in the full metabolic effects seen in squirrels, but the team discovered that boosting the uptake of adenosine in the rats' brains lowered their core body temperatures. Furthermore, with the adenosine drug, there were none of the adverse effects usually associated with hypothermia, such as shivering and metabolic stress. "That's really exciting because the adenosine mechanism is remarkably effective," says Drew. Her enthusiasm is linked to the fact that, in humans, induced hypothermia is used to treat cardiac arrest – and has the potential to treat strokes too – but the drugs currently given to suppress shivering don't work at very low temperatures.

17. Another researcher focusing on adenosine is Domenico Tupone at Oregon Health and Science University. He believes it is the key to the metabolic anomaly at hibernation's heart, which he calls "thermoregulatory inversion". In mammals, the normal physiological response to plunging temperatures is for the body to turn to brown fat, which is packed with mitochondria that make energy and generate heat. But during hibernation, the opposite happens: cooling inhibits heat production and warming boosts it. Tupone and his team found that they could induce thermoregulatory inversion in rats by giving them drugs that activate adenosine pathways. "Rats are similar to humans in terms of the internal circuitry of the brain," says Tupone. "What we suspect is that this circuit is also present in humans, but we have lost the ability to trigger it."

18. Other researchers have homed in on a small part of the brainstem called the raphe pallidus, which helps control automatic bodily processes. Matteo Cerri at the University of Bologna, Italy, and his colleagues found that inhibiting the neural activity of this region in rats and pigs can lead to a state of hypothermia that resembles torpor in hibernators. The researchers have also shown that the raphe pallidus receives signals from the hypothalamus, another key brain region for controlling hibernation. "All this computation about our

Black bears suppress their metabolism without a big drop in temperature

(Source © Stan Tekiela Author/Naturalist/Wildlife Photographer/Getty Images)

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metabolic and energetic state comes down from the hypothalamus, which is a higher region of the brain, and goes into an older region of the brain, the brainstem," says Cerri. "There, it hits this raphe pallidus region, which will then organise the body's response."

19. Cerri, Tupone and Drew hope that, as we learn more about the neuroscience of hibernation, we can go beyond turning down heat production to controlling metabolism in other ways. The ultimate prize would be a novel approach to boosting longevity. Decades of research on caloric restriction and fasting have revealed a strong link between metabolism and lifespan. In particular, we know that when nutrients are scarce, a network of metabolic pathways switches from stimulating cell growth to suppressing it, boosting repair and feeding off cellular detritus that would normally cause the cellular damage that results in ageing. Hibernators live longer than non-hibernators of the same size, and new research in both bats and marmots shows that, during hibernation, their bodies age more slowly. This suggests that a better understanding of torpor could provide new insights for anti-ageing researchers.

20. In the future, drugs might be created that could influence the neural activity involved in hibernation. It might even be possible to do this using the environmental factors that natural hibernators rely on, like the time of year or fasting, says Cerri. There is a long way to go to fully map out and target the brain circuits involved, but it is already becoming clear that we needn't be hibernators to reap the rewards. "These processes may have evolved to optimise metabolic plasticity for an animal's health during periods of torpor," says Regan. "But those processes don't necessarily need torpor to be elicited, or to have some benefit."

21. While hibernations mysteries still abound, our efforts to better understand it are finally beginning to gather momentum – and we are now waking up to the potential benefits. "People have been studying hibernation for at least a century," says Carey, "But new technologies are making things a lot easier to get at scientifically. This field is too important to not try to get as far as we can."

(Source: Alex Wilkins, New Scientist, 15 October 2022)