How hibernators might one day solve medical problems

As autumn arrives, some people in northern climes dream of spending the winter in bed. But unlike many species, we cannot hibernate. How is it then that some animals can temporarily go into a state of suspended animation, and can human medicine learn anything from them?

Hibernation, a prolonged, deep torpor characterised by a profound decrease in metabolism and body temperature, is studied by a handful of researchers around the world. Kelly Drew (Institute of Arctic Biology, Fairbanks, AK, USA), for example, studies arctic ground squirrels, a species whose core body temperature can cool to -2·9°C during hibernation. "Their heart rate falls from 200 beats per minute to 3–5", she explains, "their metabolism slows right down, and there are numerous other reversible physiological changes."

Drew is interested in what these animals can tell us about protecting the brain from ischaemia. "Hibernators can survive greatly reduced blood flow in the brain without neurological damage", she says. "If we can find how they do this, maybe we could use this knowledge to help people survive strokes or traumatic brain injuries." John Hallenbeck (National Institute of Neurological Disorders and Stroke, NIH, Bethesda, MD, USA) also sees hibernation as a system in which to study natural tolerance to ischaemia. "During hibernation, brain blood flow is at a level that would cause rapid autolysis of brain cells in non-hibernators. Even after months of hibernation there is no sign of ischaemic damage", he notes. "If we could work out how this extraordinary state is regulated, if we knew how to turn down the brain's requirement for oxygen delivery and blood flow, we might win time in which to lyse the clot after a stroke and hopefully salvage brain tissue that would otherwise be lost."

The brain is not the only organ that survives oxygen deprivation intact in hibernators. Fritz Geiser (University of New England, Armidale, Australia) and Larry Wang (University of Alberta, Edmonton, Canada) are interested in heart physiology. "Hearts from hibernators work at lower temperatures than those from non-hibernators", explains Geiser, who has investigated the effect of cooling on isolated hearts. "Hearts from hibernators keep pumping down to 0°C or below but those from non-hibernators stop at a much higher temperature. This has implications for human heart surgery, when hearts are routinely cooled to 23°C or thereabouts; any lower and they begin to fibrillate", says Geiser. If hearts could be cooled further, surgeons might have more time to operate, he says.

Oxford Scientific Films

Arctic ground squirrel (awake)

Wang has also compared hibernator and non-hibernator hearts. "An isolated rat heart can survive at 5°C for only 8 h without loss of function on rewarming", he explains, "but a ground squirrel's heart can survive for more than 24 h in the same conditions." Wang found that the regulation of intracellular calcium was very important for survival of ground squirrel hearts and has extended rat heart survival to 16 h by minimising intracellular cardiac calcium before cold storage. "If we could apply this approach to human hearts, it might extend storage times before transplantation", suggests Wang.

Ken Storey (Carleton University, Ottawa, Canada), who is studying the biochemical mechanisms behind the physiological changes of hibernation, also thinks that studies on torpor may improve transplantation success rates. "Hibernators somehow shut down their metabolism. If we could do the same with donor organs, we could store them for longer in the cold before transplantation. Currently, we take donor organs, we put them on ice, and then we try to get them where they are needed before they die. Meanwhile, there are hibernating ground squirrels whose organs work perfectly at 5°C, right on our doorstep. The cells of hibernators are almost the same as ours. Yet, when our cells are cooled from 37°C to 5°C, they go nuts in metabolic terms and those of hibernators take a nap." Surprisingly few new genes seem to be expressed in hibernation and so Storey believes that in hibernators banks of stress-activated kinases switch protein functions on and off in a coordinated, reversible way to turn down metabolism. "And the switches that can do the ground squirrel trick must also be in our cells", he says.

If Storey is right and hibernation is regulated by cellular switches, is there a master switch that starts the whole process? Many researchers remain unconvinced that such an initiating signal has been identified but Peter Oeltgen (University of Kentucky, Lexington, KY, USA) believes he has isolated a candidate from the plasma of several hibernators. "Hibernation-inducing trigger—HIT—induces a state similar to hibernation when injected into summer-active hibernators and seems to have an opiate-like effect on primates", he explains. Furthermore, pretreatment with HIT extends the life of non-hibernating animal organs in a multi-organ perfusion system, a result that could be of use in transplantation, and decreases the infarct volume in a rat-heart ischaemia model. Oeltgen, who has been working on HIT since the early 1980s, now has a cDNA for HIT and hopes to develop the protein for treatment of ischaemic injury in people.

For now, many questions remain about the physiology of hibernation. For example, which comes first in the establishment of hibernation: a reduction in metabolic rate or a reduction in body temperature or is some more complicated combination of events involved? And is hibernation an ancient response to hard times or one that has developed independently in many species? Whether physiological information from hibernating ground squirrels can be used to reduce ischaemic damage in people may depend on the answer to this question.

These and many other questions will need to be answered before the medical potential of studies on hibernation can be fully realised and the experiments will not be easy to do or to interpret. But, says Storey, "one day what we find out about hibernators will break through into mainstream science and suddenly people will be saying: 'I get it, we should be modifying this protein in this pathway in this way if we want to minimise stroke damage or improve organ preservation for transplantation'".

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