Hibernating chipmunk's brain senses loss of energy

The vast majority of mammals maintain their body temperature around 40°C throughout their lifetimes; however, hibernating mammals are an exception. Hibernation is an important adaptation to survive harsh conditions, such as frigid environments or starvation. It is an extraordinary phenomenon, involving major changes in an animal's physiology. If we unveil the mysteries of hibernation, we may be able to apply the resulting technologies to "cold sleep" (cryonics) in humans, often described in scientific fiction.

One hibernating animal, the chipmunk, lowers its body temperature to nearly 0°C, such that it feels cold to touch, and its heartbeat to approximately once per minute during hibernation. Thus, chipmunk tissues and cells are exposed to low temperatures, as well as oxygen and glucose deficiencies. The cellular metabolic rate of glucose, lipids, and proteins must be downregulated to adapt to and tolerate these conditions.

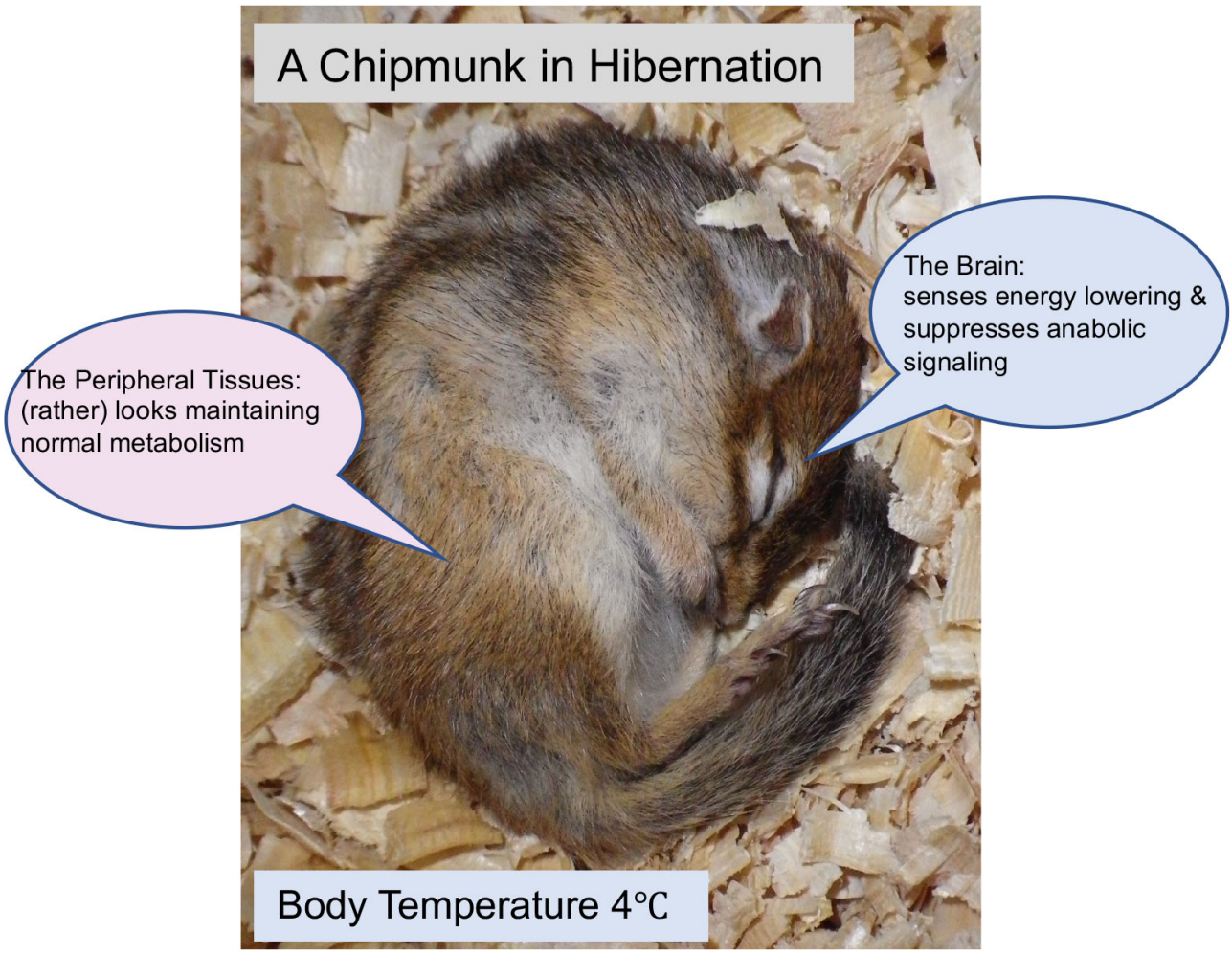

Fig. 1.

It’s still been a mystery how does hibernation start and what is the trigger of hibernation. One crucial development was finding hibernating proteins in chipmunks. Hibernating proteins are produced in the liver and work in the brain during hibernation. This suggests that hibernation might be triggered in the brain. Therefore, we compared energy-sensing signaling and protein synthesis (a major anabolic pathway) in the brain compared to the peripheral organs of chipmunks.

AMP-activated protein kinase (AMPK) is a key energy sensor. It senses the insufficiency of ATP, an energy currency in the cell and is thereby activated. Thus, lack of nutrients and oxygen activates AMPK. Upon activation, AMPK promotes energy-generating pathways such as autophagy and inhibits energy-consuming anabolic pathways such as fatty acid synthesis, gluconeogenesis, and protein synthesis by suppressing mammalian target of rapamycin (mTOR) complex 1 (mTORC1).

Although blood glucose levels were reduced to less than half in hibernating chipmunks, AMPK activity was increased only in the brain (cerebral cortex), but not in the liver and skeletal muscle. Phosphorylation of acetyl-CoA carboxylase, a substrate of AMPK was also enhanced only in the hibernating brain, indicating it’s inactivation and suggesting the suppression of fatty acid synthesis. At the same time, mTORC1 and eukaryotic elongation factor 2 (eEF2) activities were reduced in the hibernating brain, suggesting the downregulation of protein synthesis in the hibernating brain. Protein synthesis capacity was lower in the hibernating brain than in that of active chipmunks. Conversely, liver protein synthesis rate did not differ between the active and hibernating chipmunks. These results strongly suggest that metabolic downregulation accompanying hibernation emerges in the brain, at least in the early stage of hibernation.

Hibernating proteins are the member of C1q family that include adiponectin and adiponectin is known to induce AMPK phosphorylation (=activation). We now hypothesize the following scenario:

> Hibernating proteins penetrate the brain in a circannual rhythm.
> Hibernating proteins activate AMPK and suppress metabolism via an unidentified receptor.
> The brain, stimulated by the hibernating proteins, imposes overall metabolic changes and lowers body temperature.

Although it will be a long journey to understand the whole picture of hibernation, our results provide directions for further investigation.

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hibernating chipmunks
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