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## Settling down for a long winter's nap

### Focus on “Coordinate expression of the PDK4 gene: a means of regulating fuel selection in a hibernating mammal”

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HIBERNATING MAMMALS utilize efficient physiological mechanisms to minimize energy consumption during the winter. The process involves not only a decrease in the overall metabolic rate, but also a metabolic shift from preferential use of carbohydrates to triacylglycerols. In this online release of *Physiological Genomics*, Buck et al. (Ref. 1; see page 5 in this release) detail one such metabolic shift in the 13-lined ground squirrel, *Spermophilus tridecemlineatus*, which enables it to utilize free fatty acids as a primary energy source during the coldest months of hibernation.

Euthermic animals (i.e., in an active state characterized by maintenance of a constant high body temperature) oxidize carbohydrates as their primary energy source. The pyruvate dehydrogenase kinase isoenzyme 4 (PDK4), found primarily in heart and skeletal muscle, phosphorylates the pyruvate dehydrogenase complex, reducing the rate of oxidation of glucose. Insulin inhibits PDK4; during the active months of the year, then, mammals have high insulin levels and low PDK4 levels.

Hibernating mammals have drastically lowered body temperatures, a depressed metabolic rate, and are largely immobile, which decreases their energy requirements. As animals prepare for hibernation, they switch from carbohydrate oxidation to oxidation of fatty acids, which are their primary source of energy during the winter. During the winter months their hibernation is characterized by alternating periods of torpor and arousal (interbout arousal, or IBA). These IBAs consume most of the energy required during the hibernation season. Heat is generated for rewarming

and maintenance of a euthermic body temperature for 1 or 2 days. Most hibernators do not feed during IBA, even if food is available. They entirely depend upon body lipid stores accumulated during summer months. This indicates a programmed seasonal reversal of metabolic pathways for lipid handling, i.e., a switch from lipid storage in summer to lipid release in winter.

To determine the role of these key metabolic proteins in the hibernation physiology of the 13-lined ground squirrel, Buck et al. measured seasonal alterations in the mRNA and protein of both PDK4, which they had previously cloned, and insulin, which they cloned and sequenced for this study. They found the highest levels of PDK4 during hibernation in heart and skeletal muscle and in white adipose tissue (WAT); levels of PDK4 mRNA and protein were correlated. Interestingly, however, levels of pancreatic insulin mRNA did not correspond to levels of serum insulin and also appeared at odds with the metabolic state of the hibernating animals. At the onset of hibernation, levels of serum insulin remain high even as levels of PDK4 are increasing, which is paradoxical, given the inhibitory effect of insulin upon PDK4. As hibernation continues, levels of serum insulin drop despite a gradual increase in insulin mRNA levels in the pancreas. The authors suggest that this rise in insulin mRNA reflects the animal's preparation for the metabolic demands of the spring posthibernation state.

How, then, can PDK4 levels increase at the onset of hibernation? Buck et al. suggest that there are two pathways at work. They hypothesize that peroxisome proliferator-activated receptor  $\alpha$  (PPAR $\alpha$ ), a transcription factor which plays a key role in upregulating the pathways of fatty acid oxidation necessary for fuel during hibernation, also stimulates transcription of PDK4 at the onset of hibernation, despite the inhibitory presence of lingering high insulin levels. In this manner, PPAR $\alpha$  could provide the key link between these two regulatory processes at play in hibernating

Article published online before print. See web site for date of publication (<http://physiolgenomics.physiology.org>).

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mammals. They propose a model in which pancreatic triacylglycerol lipase in the WAT breaks down stored triacylglycerols to make long-chain free fatty acids, which are ligands for PPAR $\alpha$ , available. Pancreatic triacylglycerol lipase is one of two types of lipase present in WAT and is not inhibited by insulin levels. Thus, at the onset of hibernation in October, PPAR $\alpha$ , stimulated by free fatty acids, may initiate expression of PDK4 even though serum insulin levels are still high.

The findings presented by Buck et al. provide new insights into the seasonal metabolic control of hiberna-

tors. In addition, they provide a new example of the admirable capability of animals to deliberately redirect lipid storage and lipid release. Other examples of this behavior are found in breeding penguins or migratory birds. Humans apparently lack this ability, and a better knowledge of hibernators may therefore be helpful for human obesity research.

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