Integrative and Comparative Biology
Integrative and Comparative Biology, volume 54, number 3, pp. 439–442
doi:10.1093/icb/icu085
Society for Integrative and Comparative Biology

THEME AND VARIATIONS: HETEROTHERMY IN MAMMALS

Theme and Variations: Heterothermy in Mammals

Sandra L. Martin[1],* and Anne D. Yoder†

*Department of Cell and Developmental Biology, University of Colorado School of Medicine, Aurora, CO 80045, USA;
†Department of Biology, Duke University, Durham, NC 27708, USA

[1]E-mail: Sandy.Martin@ucdenver.edu

Synopsis This collection of articles is focused on the evolutionary dynamics of heterothermy in mammals, specifically torpor and hibernation. Topics cover a wide range from evolutionary genetics, physiology, ecology, and applications to human health.

Introduction

Heterothermy in mammals, that is, daily torpor and hibernation, is used by a phylogenetically diverse group of species. Although the phenotype is remarkably variable both within (Wilz and Heldmaier 2000; Gur et al. 2009; Russell et al. 2010; Rojas et al. 2014) and among species (Geiser and Ruf 1995), it is uniformly considered to be an adaptation for conserving energy in the face of stressful environmental temperatures and limiting resources. Mammalian heterothermy is both physiologically and behaviorally complex; the metabolic depression of daily torpor and hibernation can be considered as a continuum in which torpor is defined by reduced body temperature and by metabolic rate lasting less than 24 h. True hibernation is distinguished by phases of torpor that are maintained for more than 24 h, from several days to several weeks.

Hibernation is a cyclical, typically winter-season phenotypic state marked by a diverse suite of physiological characteristics. These include markedly depressed metabolic, respiratory, and heart rates and low core body temperature; remarkably, sometimes core body temperatures are even maintained slightly below freezing (Barnes 1989). Hibernators also sustain prolonged periods of physical inertia, reduced or absent intake of nutrients and water, and extended periods of ultra-low voltage brain-wave activity (Carey et al. 2003). Despite months of inactivity, hibernators emerge each spring without incapacitating atrophy of bone or muscle through disuse (Carey et al. 2003). Hibernators are distributed rather randomly across the vertebrate evolutionary tree, occurring in species as diverse as lizards, birds, and mammals. Within mammals, hibernating species are found in all three of the main branches of the Mammalia: monotremes, marsupials, and eutherians. Among the eutherians, there are hibernating species in the Orders Carnivora, Rodentia, Afrosoricida, Chiroptera, Erinaceomorpha, and Xenarthra (McKechnie and Mzilikazi 2011). This remarkable physiological plasticity also occurs in one small clade within the Primates, one that includes the dwarf lemurs and mouse lemurs of Madagascar (Dausmann et al. 2004; Blanco et al. 2013).

Historically, hibernation was observed to be a seasonal response to low temperatures, and indeed, the majority of hibernators are found in cold environments. Even so, there are numerous species found in tropical and subtropical climates that show the same extreme physiologically plastic characteristics of winter hibernation (Boyer and Barnes 1999; McKechnie and Mzilikazi 2011). Thus, investigators are increasingly thinking of torpor and hibernation as flexible metabolic responses to limited resources and as strategies conserving energy for future demands rather than exclusive behaviors that save energy in response to cold environments (Heldmaier et al. 2004; Dausmann et al. 2005). In addition to elucidating the evolutionary and ecological significance of hibernation, researchers are targeting the molecular and physiological components of hibernation to unveil factors that confer biological protection against low body temperature and lowered metabolic rate (Bouma et al. 2012). Results derived from this research can ultimately provide the tools to

Advanced Access publication June 19, 2014

chemically or genetically induce various aspects of the hibernation state in non-hibernators, thereby raising the tantalizing possibility of induced torpor and hypothermia in humans, perhaps with far-reaching medical implications. The best chance to revolutionize biomedicine, however, depends on investing in the discovery of the natural processes used in a diversity of mammalian hibernators to achieve their astonishing control of reversible metabolic suppression and of the protection of tissues (Carey et al. 2012).

Multiple physiological systems are involved in hibernation. Hibernation can be broken down into three distinct phases: preparation, entrance, and torpor. During the *preparation* phase, fat accumulates via an increased adiposity set point, food intake is elevated, metabolic rate is lowered, insulin level is increased, and lipoprotein activity is modified in various ways. *Entrance* is marked by diminished activity of the central nervous system, reduced blood flow and blood pressure, as well as by a marked transition in brain-wave activity via initiation of non-REM sleep with episodic breathing. There is an accompanying cascade of down-regulated metabolic functions. Finally, *torpor* is manifest by reduced whole-body metabolism, non-shivering thermogenesis, reduced RNA synthesis, and inhibition of protein translation via polysome disassembly and inactivation of eukaryotic translation initiation factor-2 (Boyer and Barnes 1999). During the torpor phase, torpor is punctuated by brief bouts of arousal to euthermic conditions. This pattern of inter-bout arousal (IBA) persists throughout the hibernation period, whether in cold-adapted or tropical hibernators, and is characterized by a remarkable periodicity and adherence to day-length cycles. Evidence continues to accumulate that demonstrates the complex role of gene regulation at multiple sites across the genome in orchestrating the initiation, maintenance, and synchronization of the three phases of the hibernation response, including IBAs.

Summary of the symposium

This collection on torpor and hibernation comprises six articles, four of which are reviews; the remaining two test ecological and evolutionary hypotheses with new data.

New data reported by Zervanos et al. (2014) address the so-called hibernation-optimization hypothesis. The deep torpor of hibernation, while advantageous for saving large amounts of energy, that is, up to 98% of what would otherwise be required for overwintering (Heldmaier et al. 2004), is not without risk in an evolutionary sense. Specifically, a torpid hibernator will never manage to mount a response quickly enough to escape from a predator, and there may be other costs as well. Given that hibernation and, specifically, time spent in torpor, is an energy-saving strategy, then the energy-optimization hypothesis predicts that animals will avoid the use of torpor if stores of energy are sufficient, that is, the greater the energy stores of an animal, the less time it will spend in torpor. One simple test of this prediction is to determine whether animals with more fat spend less time in torpor. In this issue of *Integrative and Comparative Biology*, Zervanos et al. (2014) examine the relationship between body mass (shown in other work to be highly correlated with fat stores) and time in torpor versus euthermia. Data on body temperature were captured using implanted dataloggers over 12 hibernation seasons in 50 free-living woodchucks in northeastern United States. The body weights of the animals at the onset of hibernation and time spent in torpor versus euthermia indicate that as body mass increases, the time in torpor decreases (and thus time euthermic increases), a result consistent with the hibernation-optimization hypothesis.

Phenotypes, even complex behavioral phenotypes, ultimately arise from the expression of genes. The phylogenetically dispersed distribution of hibernators calls into question several important aspects of the homology of hibernation, and the genetic and environmental controls that trigger and maintain the hibernating state. There are two possibilities: (1) hibernation is an ancestral vertebrate condition that has been “turned off” in the majority of vertebrate species or (2) it is a derived condition that has evolved multiple times by convergent evolution. In either case, it is of fundamental interest to discover the genetic controls that trigger and maintain hibernation. It follows that a way to gain molecular understanding of the hibernating phenotype is to identify differentially-expressed or highly adapted genes in eutherian hibernators. Villanueva-Cañas et al. (2014) take a comparative genomics approach to examine patterns of differential expression and gene evolution in hibernators from different lineages compared with non-hibernators. Despite the difficulties of working with genomic sequences that were incomplete or of poor quality in some of these species, and problems caused by variability among the studies in how hibernation states were defined or the low numbers of distinct states that were examined, at least two key findings emerged from the analysis. First, although specific hibernation-expressed genes were not significantly shared among the different species, their gene networks were, indicating that a set of common pathways are important for hibernation (e.g., fat catabolism/beta-oxidation). Second, no genes with evidence of positive selection for hibernation were found, either in a broad screening approach, or in a more specific screen of manually curated "hibernation-related" genes. This may support the hypothesis that the hibernation phenotype derives from the differential expression of common mammalian genes (Srere et al. 1992), but, due to the limitations, both of the genomic and of the differential-expression data, additional work along these lines will be important in the future.

Doherty et al. (2014) provide a comprehensive metabolism-centric review of mechanisms underlying bone homeostasis in hibernators. Bone homeostasis depends on the equilibrium between the formation and resorption of bone, that is, balance between the actions of osteoblasts and osteoclasts. Typically, disuse and starvation, both experienced by hibernators for months, lead to an imbalance and loss of bone. The molecular mechanisms underlying energy metabolism in non-hibernators are becoming increasingly well understood and this review attempts to integrate these findings into the context of bone homeostasis in hibernation. The reader who is eager for detail is cautioned to pay close attention to the exact physiological status of the animals in the cited primary literature. Because of the intrinsic cycle-within-a-cycle nature of hibernation in the obligate hibernators (Serkova et al. 2007), timing across the year and within torpor-arousal cycles can have a large impact on measured values of hormones, metabolites, and proteins. Variability in these factors, especially when uncontrolled, can lead to problems with generalizations and even can result in apparent contradictions among studies.

A review of acid-base physiology by Malan (2014) thoughtfully illustrates how hypercapnic acidosis can lead to the hypometabolic state. The relationships between mammalian hibernation and other states of reduced metabolism in non-mammalian vertebrates and in invertebrates are highlighted, leading to the conclusion that this mechanism of metabolic inhibition is a retained ancestral trait. A provocative argument is made that the link between natural mammalian hibernation and the "pH-stat" procedure, used for acid-base control under conditions of artificial hypothermia in some patients, could help refine and inform our understanding of both.

This link between natural metabolic depression, as seen in hibernation and clinical application, is further developed in the review article by Quinones et al. (2014), who argue that ability to meet cellular and organismal demands for energy is a critical requirement for survival not only of animals in the wild, but also of critically ill patients. Thus, in the face of reduced supply, organisms must either invest more energy in finding and procuring the limited resources or lower their energetic demand. Most clinical interventions at the moment are aimed toward increasing supply, but based on natural solutions to the same types of supply-and-demand problems, lowering demand may prove more fruitful. Particularly, hibernators excel at engineering reversible metabolic depression and protecting their organs from ischemia-reperfusion type injuries. This article relates current clinical problems and management strategies to mechanisms of natural hypometabolism in torpor and hibernation.

A different angle on the questions of resource allocation and hibernation-optimization is considered by McAllan and Geiser (2014) who review the use of heterothermy during reproduction. Initial studies of hibernation in sciurid rodents and hamsters provided ample evidence that torpor and reproduction were mutually exclusive. Yet, as more species that use heterothermy are studied, there is an increasing appreciation that reproduction and heterothermy are not mutually exclusive, and that it may even be optimal under some conditions to reproduce while exploiting the savings in energy afforded by the use of torpor. Interestingly, utilization of torpor generally slows reproduction, and reproduction alters torpor such that it occurs less frequently and at a higher temperature. Given the wide variations in natural history and heterothermic behavior among mammals, perhaps it should not be surprising that the answer to the question, "is torpor compatible with reproduction?" is "it depends".

Most of the papers presented in this symposium raise as many questions as they answer, but so it goes when we are attempting to understand a mammalian phenotype that reflects such a complex brew of organism–environment interactions. Mammalian heterothermy is a theme with many variations. To identify the theme, we must first tackle the variations.

References

Barnes BM. 1989. Freeze avoidance in a mammal: body temperatures below 0°C in an arctic hibernator. Science 244:1593–5.

Blanco MB, Dausmann KH, Ranaivoarisoa JF, Yoder AD. 2013. Underground hibernation in a primate. Sci Rep 3:1768.

Bouma HR, Verhaag EM, Otis JP, Heldmaier G, Swoap SJ, Strijkstra AM, Henning RH, Carey HV.

2012. Induction of torpor: mimicking natural metabolic suppression for biomedical applications. J Cell Physiol 227:1285–90.

Boyer BB, Barnes BM. 1999. Molecular and metabolic aspects of mammalian hibernation. Bioscience 49:713–24.

Carey HV, Andrews MT, Martin SL. 2003. Mammalian hibernation: cellular and molecular responses to depressed metabolism and low temperature. Physiol Rev 83:1153–81.

Carey HV, Martin SL, Horwitz BA, Yan L, Bailey SM, Podrabsky J, Storz JF, Ortiz RM, Wong RP, Lathrop DA. 2012. Elucidating nature's solutions to heart, lung, and blood diseases and sleep disorders. Circ Res 110:915–21.

Dausmann KH, Glos J, Ganzhorn JU, Heldmaier G. 2004. Hibernation in a tropical hibernator. Nature 429:825–6.

Dausmann KH, Glos J, Ganzhorn JU, Heldmaier G. 2005. Hibernation in the tropics: lessons from a primate. J Comp Physiol B Biochem Syst Environ Physiol 175:147–55.

Doherty AH, Florant GL, Donahue SW. 2014. Endocrine regulation of bone and energy metabolism in hibernating mammals. Integr Comp Biol 54:463–83.

Geiser F, Ruf T. 1995. Hibernation versus daily torpor in mammals and birds: physiological variables and classification of torpor patterns. Physiol Zool 68:935–66.

G1ur MK, Refinetti R, Gur H. 2009. Daily rhythmicity and hibernation in the Anatolian ground squirrel under natural and laboratory conditions. J Comp Physiol B 179:155–64.

Heldmaier G, Ortmann S, Elvert R. 2004. Natural hypometabolism during hibernation and daily torpor in mammals. Respir Physiol Neurobiol 141:317–29.

Malan A. 2014. The evolution of mammalian hibernation: lessons from comparative acid-base physiology. Integr Comp Biol 54:484–96.

McAllan BM, Geiser F. 2014. Torpor during reproduction in mammals and birds: dealing with an energetic conundrum. Integr Comp Biol. 54:516–32.

McKechnie AE, Mzilikazi N. 2011. Heterothermy in afrotropical mammals and birds: a review. Integr Comp Biol 51:349–63.

Quinones QJ, Ma Q, Zhang Z, Barnes BM, Podgoreanu MV. 2014. Organ protective mechanisms common to extremes of physiology: a window through hibernation biology. Integr Comp Biol 54:497–515.

Rojas AD, Körtner G, Geiser F. 2014. Torpor in free-ranging antechinus: does it increase fitness? Naturwissenschaften 101:105–14.

Russell RL, O'Neill PH, Epperson LE, Martin SL. 2010. Extensive use of torpor in 13-lined ground squirrels in the fall prior to cold exposure. J Comp Physiol B 180:1165–72.

Serkova NJ, Rose JC, Epperson LE, Carey HV, Martin SL. 2007. Quantitative analysis of liver metabolites in three stages of the circannual hibernation cycle in 13-lined ground squirrels by NMR. Physiol Genomics 31:15–24.

Srere HK, Wang LCH, Martin SL. 1992. Central role for differential gene expression in mammalian hibernation. Proc Natl Acad Sci USA 89:7119–23.

Villanueva-Cañas JL, Faherty SL, Yoder AD, Albà MM. 2014. Comparative genomics of mammalian hibernators using gene networks. Integr Comp Biol 54:452–62.

Wilz M, Heldmaier G. 2000. Comparison of hibernation, estivation and daily torpor in the edible dormouse, *Glis glis*. J Comp Physiol B 170:511–21.

Zervanos SM, Maher CR, Florant GL. 2014. Effect of body mass on hibernation strategies of woodchucks (*Marmota monax*). Integr Comp Biol 54:443–51.