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The Hibernation Continuum: Physiological and Molecular Aspects of Metabolic Plasticity in Mammals

Frank van Breukelen,[1] and Sandra L. Martin[2]

[1]School of Life Sciences, University of Nevada, Las Vegas, Nevada; and [2]Department of Cell and Developmental Biology, University of Colorado School of Medicine, Aurora, Colorado
sandy.martin@ucdenver.edu

Mammals are often considered to be masters of homeostasis, with the ability to maintain a constant internal milieu, despite marked changes in the environment; however, many species exhibit striking physiological and biochemical plasticity in the face of environmental fluctuations. Here, we review metabolic depression and body temperature fluctuation in mammals, with a focus on the extreme example of hibernation in small-bodied eutherian species. Careful exploitation of the phenotypic plasticity of mammals with metabolic flexibility may provide the key to unlocking the molecular secrets of orchestrating and surviving reversible metabolic depression in less plastic species, including humans.

Patterns of Heterothermy in Mammals

In birds and mammals, endothermy is defined as an increase of resting or routine oxygen consumption that is ~5- to 15-fold higher than that observed in similar sized ectotherms (89). The result of this increased metabolism is an increased body temperature (T_b). Conversely, decreased metabolism is accompanied by reduced T_b. Modification of the thermoregulatory setpoint in mammals allows for control of both T_b and metabolism (29); when the setpoint is lowered to approach an ambient temperature that is below T_b, both metabolism and T_b decrease. Hibernation lies at the extreme end of a broad spectrum of phenotypes in endotherms that conserve energy by lowering metabolism and hence T_b (FIGURE 1).

Slow-wave sleep is considered the most shallow form of metabolic depression and is common to all mammals (4). T_b is only slightly depressed (FIGURE 2A), and oxygen consumption is reduced just 10-15% in this state (95). Torpor is a deeper form of metabolic depression that can be expressed in a variety of patterns. In daily torpor, core T_b is usually moderately depressed below 33°C for relatively short periods of time, e.g., <24 h (FIGURE 2B). In the white-footed mouse, *Peromyscus leucurus*, effective daily torpor use can result in an energetic savings of 74% (85). The most extreme form of metabolic depression in mammals occurs during deep hibernation (FIGURE 2C), as exemplified by small-bodied, temperate-zone species from a wide range of taxa (reviewed in Refs. 7, 70). In some hibernators, oxygen consumption decreases to as low as 1% of active rates and T_b to as low as −2.9°C (2), leading to a seasonal energy savings of as much as 90% (88). Historically, some authors have used the term *estivation* to describe torpor bouts that are longer than 1 day (characteristic of hibernation) but occur in warm dry periods rather than in the cold (93). As our knowledge of the thermoregulatory and activity patterns of different mammalian species increases (reviewed in Refs. 21, 22), so does our appreciation of the extent of their metabolic flexibility.

At this point, it is important to attempt to dispel some of the confusion surrounding the nomenclature of hibernation and torpor. Some of this confusion may be the result of the diversity of metabolic strategies underlying torpor use and of hibernation patterns. Most authors refer to torpor as a physiologically controlled depression of metabolic rate and activity. Torpor initiates with a regulated lowering of heart, respiratory, and metabolic rates as well as T_b setpoint, which allows T_b to approach ambient temperature (FIGURE 2, B AND C). After a period of low metabolic activity and stable, but lowered T_b, the animal elevates heart, respiratory, and metabolic rates to initiate rewarming and restoration of active T_b, recovering from torpor (FIGURE 2B). Many species use torpor to conserve energy during their daily periods of inactivity; this pattern of torpor utilization is daily torpor or daily heterothermy (FIGURE 2B). Here, we will use the terms “daily torpor” and “daily heterothermy” interchangeably. In contrast to the pattern in daily heterotherms, torpor bouts in deep hibernators have classically been defined as extending to longer than 1 day; these are typically confined to the cold or dry season when food resources become limiting. Given that hibernation

was first described as "winterschlaf," a widely useful and historically correct definition of hibernation is "multiday bouts of torpor during winter." During deep hibernation, the multiday periods of torpor are punctuated periodically by arousals to euthermia, also known as interbout arousals, giving rise to a pattern of heterothermy (FIGURE 2C). Unfortunately, the hibernation literature is often confused by indiscriminate use of the word "hibernation" to mean the period of low T_b (e.g., torpor), the entire season of heterothermy, or both. Here, we define hibernation to be the season of torpor utilization (FIGURE 2C) and will further specify the physiologically distinct stages of hibernation, which are minimally *1*) entering; *2*) maintaining, or *3*) arousing from torpor; and *4*) interbout euthermia (IBE; FIGURE 2D).

The physiological mechanisms controlling temperature and metabolism during entry into and exit from torpor, whether they occur in the pattern context of daily torpor or hibernation, appear to be identical (Ref. 93; compare FIGURE 2, B AND D). It is important to note that, despite the shared feature of lowered T_b between mammalian torpor and hypothermia, the controlled lowering of T_b setpoint and metabolism during torpor is unique to torpor; in hypothermia, metabolic rate is elevated as T_b drops, such that a great deal of energy is expended attempting to fight the decline in T_b. This is the exact opposite of what happens during entrance into torpor. Additionally, the hypothermic mammal is unable to orchestrate a spontaneous recovery from low T_b using endogenous mechanisms (9), whereas the ability to rewarm spontaneously is a key feature of natural torpor.

Much of our knowledge about the physiology of torpor and patterns of torpor utilization in mammals originates from work on rodents. Mice and other murid rodents have been excellent models for studies of daily torpor, whereas ground squirrels and other sciurid rodents have been widely used for hibernation studies (12). As we will see, many mammals deviate in various ways from the classical patterns of hibernation seen in these models and illustrated in FIGURE 2. For instance, black bear hibernation ("denning") consists of a continuous torpor for months despite cyclical warming (Ref. 76; FIGURE 3A). Oxygen consumption during denning may be reduced to 25% of basal values. These data suggest a metabolic suppression independent of T_b. However, other indicators imply a more shallow torpor status than that of ground squirrels. In bears, there is only a moderate depression of T_b to >30°C, and females give birth and nurse their neonate(s) during the denning period. Although often cited otherwise, there are data to suggest depressed but sustained kidney function and urine production in denning bears, which is absent under normal conditions in ground squirrels (e.g., Refs. 8, 31, 38, 60). In other words, hibernation can be accompanied by markedly varying physiological attributes depending on species.

In attempting to designate hibernation vs. daily torpor sensu stricto, it is important to consider the evolutionary origins of torpor and endothermy. The predominant view in the earlier literature assumes torpor use evolved as a derived phenotypic response to survive the hardships of a boreal winter (50). These assumptions include consideration of basal mammals as maintaining high and stable T_b. However, many mammals, including marsupials, monotremes, and even some placental species such as tenrecs, are considered protoendothermic and demonstrate highly variable T_b, even during their active season (FIGURE 3B).

Tenrecs are Afrotherians and are related to elephants, manatees, elephant shrews, and hyraxes. Tenrecidae consists of some 10 genera encompassing 35 species, with all but three of these being endemic to Madagascar (1, 20). There is tremendous diversity among the tenrecs in niche, morphology, and use of torpor. These protoendotherms may be the closest extant representatives to a very early mammalian ancestor (61). Genetic and morphological studies of the evolution of placental mammals have been unable to establish a robust phylogeny. Significant support exists for at least three different origins of placental mammals; in at least one of these scenarios, Afrotherians are basal to the other placental mammals (e.g., Exafroplacentalia rooting; Ref. 68).

Several features of metabolic flexibility in mammals blur the distinctions between daily torpor and hibernation. Tenrecs highlight the difficulties in strictly delineating daily torpor vs. hibernation. Although much remains to be discovered regarding tenrec hibernation and torpor use, the available data suggest marked inter- and intra-species differences in the extent and duration of torpor use. In one study, investigators implanted temperature loggers in penned lesser hedgehog tenrecs, *Echinops telfairi* (49), and found the winter season consists primarily of daily torpor bouts. However, one individual experienced bouts of torpor that lasted up to 4 days–a period most would consider characteristic of hibernation. The data suggest these extended torpor bouts are due to large fluctuations

FIGURE 1. **A continuum of metabolic depression in mammals**
Energy consumption from least (dark blue, hibernation) to most (no color, actively foraging). SWS, slow-wave sleep.

in ambient temperature and that *E. telfairi* may be changing its normal active period to exploit the energetic advantages of passive rewarming. In greater hedgehog tenrecs, *Setifer setosus*, hibernation consists of conforming largely to fluctuations in ambient temperature that include temperatures that exceed those experienced by the thermoregulating animal in the active season (47, 51). In contrast to the rather modest hibernation pattern of *E. telfairi* or *S. setosus*, the common or tailless tenrec, *Tenrec ecaudatus*, undergoes deep hibernation. Rather than choosing tree holes or shallow burrows like *E. telfairi* or *S. setosus*, *T. ecaudatus* hibernates underground (52). These animals experience low T_b throughout their extended hibernation season, with no interbout arousal that characterizes every other known deep hibernator (52). We very recently acquired a colony of *T. ecaudatus* and found that animals are consistently lethargic during the Austral winter even when housed at 28°C or handled, although the depth of this lethargy is variable (van Breukelen F, personal observations). This contrasts to the end of the hibernation season in ground squirrels, when animals spontaneously cease to orchestrate torpor bouts and return to homeothermy, i.e., they maintain a narrowly regulated and stable T_b (12, 80). On the other hand, it is similar to what is seen in bears, who, along with *T. ecaudatus*, end their hibernation season by gradual resumption of feeding and increased activity over the course of a few weeks in a state of "walking torpor." More surprisingly is that preliminary observations (van Breukelen F, unpublished observations) suggest sporadic facultative torpor or hibernation at ambient temperatures from 11 to 28°C in individual tenrecs during the active season, when their conspecifics are reproducing, eating, and generally active.

As indicated earlier, daily torpor is generally characterized by a modest depression of T_b, i.e, below 32°C (93). However, in another Afrotherian, the rock elephant shrew, *Elephantulus myurus*, T_b may become quite low (5–10°C) despite short torpor bout lengths that are <27 h (57). It would be very easy and perhaps appropriate to ascribe the Afrotherians as being atypical. However, patterns of torpor use that defy ready assignment as either daily torpor or hibernation can also be found in phylogenetically distinct species such as lemurs. Fat-tailed dwarf lemurs, *Cheirogaleus medius*, hibernate in tree holes for extended periods (as much as ~7 mo) despite ambient temperatures that may be over 30°C during the day (13, 14). These lemurs experience an apparent poikilothermy that is quite distinct from the more usual poikilothermic behavior of ectotherms, because the torpid dwarf lemur may periodically increase its T_b to above ambient temperature. Remarkably, the dwarf lemur's T_b pattern depends on its tree hole, i.e., the ambient temperature fluctations. If the tree hole is poorly insulated and its temperature regularly exceeds 30°C, the animal appears to be strictly poikilothermic, that is, T_b closely tracks the temperature of the tree hole (FIGURE 3C). If the dwarf lemur spends too many consecutive days below 30°C in a better-insulated tree hole, however, it periodically adds a boost of metabolic heat production during the rewarming phase of the daily ambient temperature cycle to drive T_b to above 30°C and above the temperature in the tree hole (FIGURE 3D). Finally, if that same animal moves to a very well insulated tree hole where the ambient temperature remains more constant and close to 20°C, the lemur's T_b rhythm looks much more like hibernation in a temperate-zone mammal, with continuous torpor at low T_b punctuated

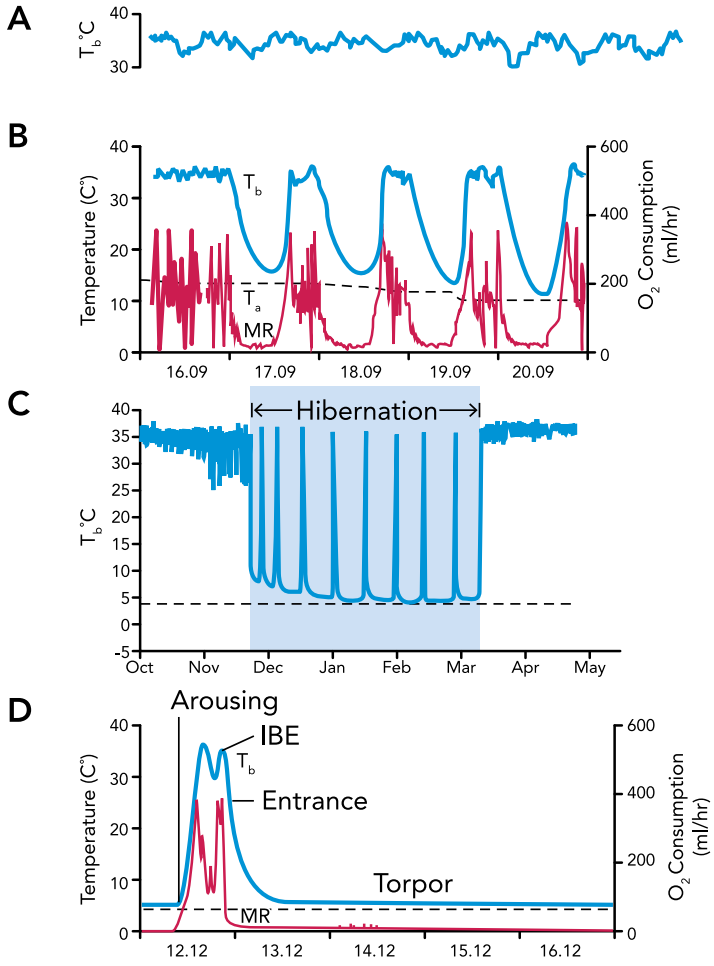

FIGURE 2. **Schematics illustrating rhythms of sleep, daily torpor, and deep hibernation**
A: 8 days in summer, golden-mantled ground squirrel (Martin SL, unpublished observations). *B*: daily torpor in *Glis glis* showing body temperature (T_b), ambient temperature, and metabolic rate (data adapted from Ref. 93). *C*: ground squirrel hibernation: T_b across 8 mo illustrates the homeothermic and heterothermic (blue shadow) periods (T_b trace is adapted from Ref. 3). *D*: metabolic rate and T_b during various hibernation phases in *Glis glis*. IBE, interbout euthermia. Data are adapted from Ref. 93. In all panels, blue lines represent body temperature, red lines represent metabolic rate, and dashed black lines represent ambient temperature.

by short arousals to euthermia (FIGURE 3E) that are driven by a large increase in metabolic rate (15). During the dry season in mouse lemurs, *Microcebus griseorufus*, there are marked inter-individual variations in torpor use that may extend from daily torpor to hibernation over the course of weeks (43, 44). Other mammals, including the marsupial *Smithopsis macroura*, also avail themselves of passive solar warming in their torpor ecology (53).

It has been argued that daily torpor and hibernation are discrete adaptations (70) rather than belong to a continuum (7) of metabolic plasticity, as illustrated in FIGURE 1. We note that the plasticity within individuals to orchestrate diverse patterns of metabolic activity and T_b, as seen with dwarf lemurs moving among different tree holes with different insulating properties (FIGURE 3, C–E; Ref. 14); dormice engaging in daily torpor, hibernation, and estivation (93); highly variable T_b patterns of ground squirrels preparing for hibernation during fall (71); seasonal changes in torpor bout duration and frequency of arousal that leads to reproducibly longer periods of torpor mid-hibernation season (23); and variable patterns of woodchuck hibernation depending on environmental conditions (97); taken together with the intermediate torpor utilization patterns of the Patagonian opossum (24) and tenrecs described above are consistent with the view that the metabolic plasticity observed among mammals represents a continuum of possible phenotypes rather than fixed discrete patterns. It is reasonable to infer that the apparent clustering of features, such as minimum T_b and metabolic rate during torpor or maximum torpor bout length, into apparently distinct pattern groups for daily torpor and hibernation (70) may reflect optimal conditions for energy conservation given specific conditions of ambient temperature and body size taken together with strategies for avoiding predation and enhancing reproduction (79, 96).

The Mysterious Periodic Arousals from Torpor That Give Rise to Heterothermy in Hibernators: Or, Why Arouse?

With the exception of the common tenrec described above, all deep hibernators, e.g., animals spending multiple days with low T_b, experience periodic arousals to euthermia between bouts of torpor (IBE; FIGURE 2; Refs. 12, 52). These periodic arousals are paradoxical because hibernation is reasonably presumed to be an energy-saving adaptation, yet at least 70% of the energy consumed over a ground squirrel's hibernation season is used to drive the periodic arousals from torpor (88). Given that so much more energy could be saved by remaining torpid continuously, why would an animal apparently waste it to repeatedly restore high T_b numerous times over a period of many months? The answer to this question remains one

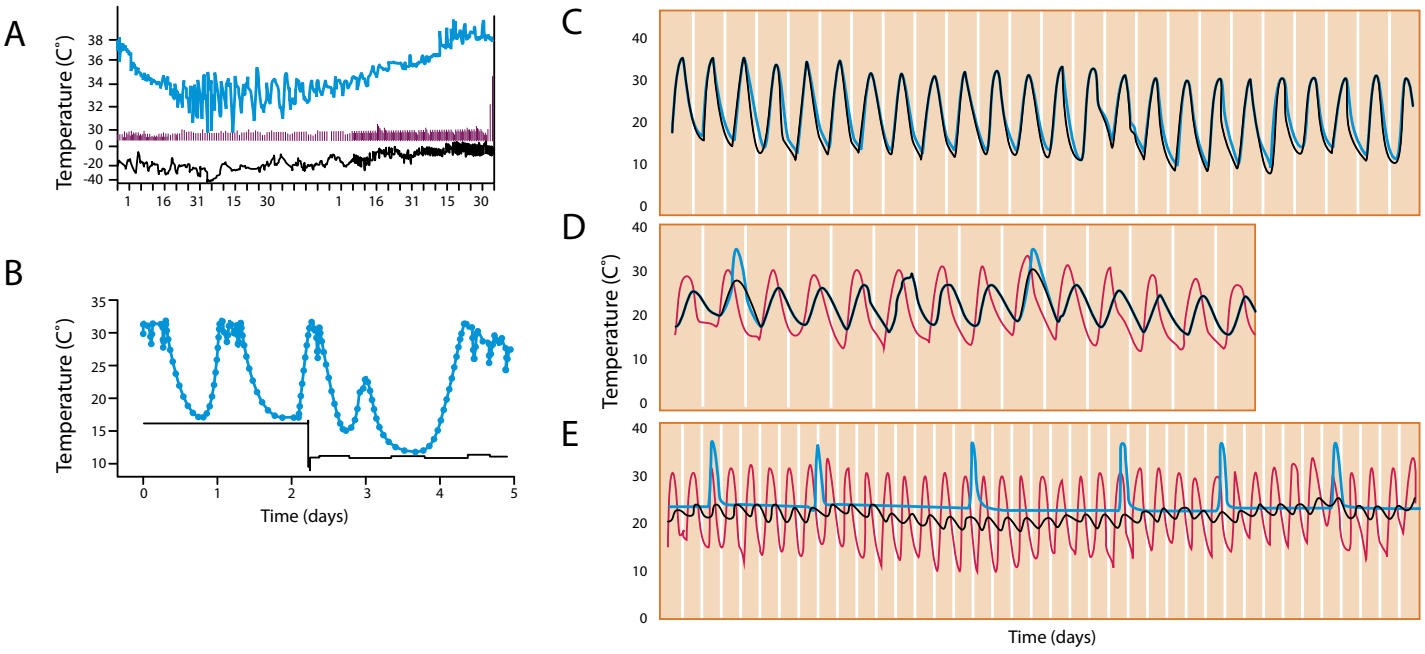

FIGURE 3. **Variation in patterns of heterothermy in mammals**
A: hibernation in black bear over ~5 mo. Figure is modified from Ref. 76 and used with permission. *B:* Tenrec body temperature flexibility and ambient temperature over 5 days (van Breukelen F, unpublished observations). *C–E*: dwarf lemurs in different tree holes, from least (*C*) to most (*E*) insulated, based on ambient temperature difference from outside to tree-hole, as described in Ref. 14. All panels, blue represents T_b, and dashed black represents T_a. In *A*, red tics show movement; in *C-E*, red lines show outside T_a vs. treehole T_a in black.

of hibernation's biggest mysteries, despite substantial speculation and research effort.

There is no question that, as a hibernator recovers from the near-freezing temperatures of torpor, the activities of cell and molecular processes that slowed at low T_b (the so-called Q_{10} effect) are rapidly elevated throughout the body, along with the more apparent physiological processes. But is this biochemical activation effectively equivalent to halting a reaction on ice and restarting it by moving it to 37°C (temperature explains both cause and effect), or is arousal actually triggered by the need to restore one or more of those processes, and, if so, which process is key? In most cases where a given process has been claimed as the reason underlying the periodic arousals, it is more likely that the process simply resumed because T_b was restored; among these are DNA, RNA and protein synthesis, cell division, various aspects of immune function, and sleep (reviewed in Refs. 12, 80). More recent findings of alterations that occur during torpor and are restored during the interbout euthermic periods include dendritic retraction (69, 86, 87), leukocyte sequestration in secondary lymphoid organs (6), receptor-mediated endocytosis (39), protein degradation in the proteasome (83), and IRES-dependent initiation of translation (63).

It has been argued for decades that the hibernator's periodic arousals from torpor are needed to rectify some imbalance that accrues at low T_b (FIGURE 4; reviewed in Ref. 54). This view is supported by the strong association of torpor bout length with total metabolism. Specifically, elevated oxygen consumption rates during torpor occur either when T_b is elevated due to higher ambient temperature or when hibernators increase metabolic heat production to maintain a near (but above) freezing T_b against ambient temperatures that are well below freezing (10). In both cases, torpor bout lengths are shortened, thereby tying torpor bout duration to overall metabolism. These data are consistent with at least two possible mechanisms: *1*) depletion or accrual of a metabolic product that causes arousal from torpor (FIGURE 4) or *2*) a lengthening of the normal circadian clock leads to a more extreme version of the standard mammalian daily activity cycle (54). Interestingly, these two seemingly disparate views may actually not be separable, since there is growing appreciation for the impact of metabolites and metabolism on the transcription/translation feedback loops that orchestrate the mammalian circadian system (16, 46, 64, 66).

If the circadian system is merely extended to specify a torpor-arousal cycle, it predicts that torpor bout length is related to a central nervous system-based timer. As depicted in FIGURE 1, daily torpor and hibernation can be considered elaborations of mechanisms evoked for slow-wave sleep (30), a view supported by the marked similarities

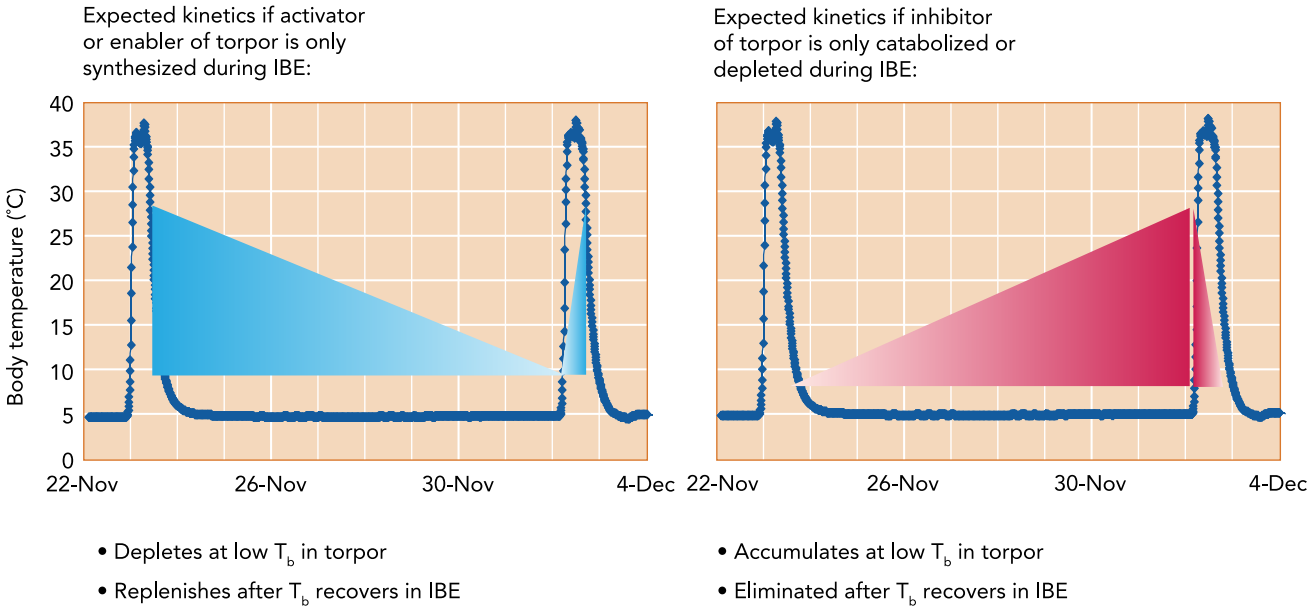

FIGURE 4. **Kinetic model of biochemical alterations determining torpor-arousal cycles**
A: a hypothetical critical inducer/enabler of torpor (blue) increases during the euthermic period and then slowly depletes over the torpor bout. *B*: conversely, an inhibitor of torpor (or activator of arousal, red) accumulates at low T_b during torpor and is eliminated during the euthermic arousal (IBE). Although definitive evidence for either an inducer or an inhibitor of torpor is lacking, there are circulating metabolites that have been shown to cycle as predicted in both *A* and *B*. Several amino acids, modified amino acids, acetoacetate, and degradation products of branched-chain amino acids deplete during torpor but are restored during each IBE (*A*) in hibernating ground squirrels. Conversely, other modified and unmodified amino acids, vitamin B metabolites, myo-inositol, and allantoin accumulate across the torpor bout and are restored to lower levels (*B*) before entrance into the next bout of torpor (17). Clearly frequent, precisely timed samples are needed to capture these types of abundance changes over the torpor-arousal cycle; metabolite and gene product dynamics will be obscured by averaging among randomly collected torpor vs. IBE samples.

between sleep and torpor physiology, e.g., reduced T_b setpoint, lowered electroencephalographic activity, and behavioral quiescence. Sleep timing and duration are greatly influenced by circadian rhythm function (11); thus it is plausible that the simplest path to evolving a timer for hibernation cycles is via adaptation of the circadian timer. The view that periodic arousals during hibernation are the result of a lengthened circadian activity-inactivity cycle was proposed long ago (54) and has since been elaborated (55). In effect, given an oscillator that is not temperature compensated, torpor bouts of hibernation can be considered 1 long circadian day (or night) at the molecular level. This view has significant merit. The canonical view of the mammalian molecular clock consists of transcription factors CLOCK and BMAL1 driving the transcription of *cryptochrome* and *period (per)* genes, which then feedback to inhibit *clock* and *bmal1* gene expression (42). Oscillations are dependent on transcription, translation, and mRNA and protein degradation; processes we know are markedly depressed during torpor in hibernating ground squirrels (81–83) and hamsters (62), and less, but nevertheless significantly, depressed in Djungarian hamsters torpid at 25°C during daily heterothermy (5).

In hibernating European hamsters, in situ hybridization of the superchiasmatic nucleus shows that *per1*, *per2*, and *Bmal1* cease to cycle in a circadian manner across torpor bouts (65). Furthermore, the mRNA hybridization intensity for arylalkylamine *N*-acetyltransferase, the clock-responsive gene that controls melatonin synthesis in the pineal gland, as well as that of arginine vasopressin are consistent with torpor being a

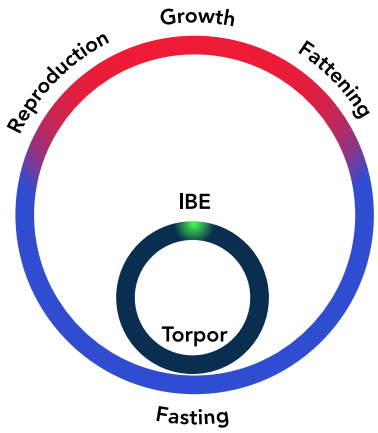

FIGURE 5. **Torpor-arousal cycles in ground squirrels are embedded in a seasonal cycle**
The circannual rhythm of hibernation is represented by the outer circle (homeothermic period in red; heterothermic, i.e., hibernation in blue), and the torpor-arousal cycle is represented by the inner circle (IBE, green; torpor, dark blue).

prolonged, continuous night phase. Unfortunately, the sampling frequency in this study was insufficient to determine whether the clock is simply slowed in torpor-arousal cycles or whether it is completely abandoned. However, gene expression changes measured by quantitative methods on RNA extracts from hibernating ground squirrels indicate that a peak of circadian gene expression occurs in the hypothalamus and in peripheral tissues during the euthermic arousals (73, 94), consistent with a possible role for this system in the timing of torpor-arousal cycles during hibernation. In contrast to these limited molecular data, however, results from careful field studies on male arctic ground squirrels seem to favor the view that the circadian system ceases to function during hibernation. Body temperature was continuously elevated but was arrhythmic for as many as 10–27 days while the animals remained sequestered in their hibernacula before spring emergence and exposure to light. Interestingly, these same males retained a free-running circadian rhythm in similar conditions after immergence into their hibernacula in the fall but before the onset of heterothermy (90–92). A more inclusive and precisely timed sampling strategy for assessment of the molecular circuitry of the circadian system during torpor-arousal cycles is needed to determine conclusively whether the clock simply stops ticking during hibernation or whether it continues with normal, albeit slowed, rhythm.

Just as deciphering the molecular components of the circadian system requires precisely timed, frequent sampling (37, 45, 48, 67), so will deciphering the molecular components of hibernation. And, like the circadian circuitry (42), hibernation circuitry is no doubt complex, with multiple levels of regulation; it clearly involves distinct gene expression responses in different organ systems throughout the body (18, 19, 25–28, 32–35, 39, 56, 73, 84, 94), which may be controlled by underlying metabolic status (17, 40, 64, 66, 72, 75, 77, 78). It is reasonable to hypothesize that interactions between changing metabolite concentrations and the core clock components lead to torpor-arousal cycles. Arousal could be caused by either depletion of a factor (or factors) critical for torpor (FIGURE 4A) or accumulation of a factor(s) inhibitory for torpor (FIGURE 4B). There is growing evidence for accumulation or depletion of certain plasma (17, 58) or liver (59, 74) metabolites during torpor. However, studies of hibernators to date have lacked the sampling precision, intensity, or depth to elucidate the key players. From FIGURE 4, it is clear that imprecise sampling will erase all chance of finding molecules with the expected kinetics of key molecular components of the cycle. The complexity of hibernation is further increased by the fact that more than one cycle may be involved, with a seasonal

cycle superimposed on the torpor-arousal cycle (FIGURE 5); key factors, e.g., the nutritional and reproductive status of the animal, vary tremendously across the season (12). Therefore, the timing of sample collection across the year is also crucial for molecular studies involving hibernators. The importance of the seasonal framework is highlighted by results of a recent study showing that muscle atrophy precedes rebuilding in hibernating 13-lined ground squirrels (36) and the finding that a seasonal change in purinergic signaling confers sensitivity to induction of torpor by an adenosine receptor agonist in Arctic ground squirrels in winter (41).

The use of a multi-species comparative approach may also facilitate elucidation of torpor timing mechanisms. In ground squirrels, there are pronounced cycles of torpor and arousal that imply a robust timing system. In common tenrecs and bears, animals remain torpid for the entire season. In dwarf lemurs, the animals must apparently reach a T_b of >30°C to maintain torpor, otherwise, they arouse. When married to an elucidated molecular model of timing, the diversity represented in these species could provide the means to resolve one of hibernation's greatest mysteries: Why arouse? Despite much speculation to the contrary, biochemical mechanisms that determine the torpor-arousal cycle are not well understood. We believe that revealing these mechanisms will be the key to engineering safe, reversible metabolic depression in humans for a wide range of applications, and hence such understanding deserves vigorous pursuit. ■

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References

1. Afrotheria Specialist Group. *IUCN Afrotheria Specialist Group* (Online). Gland, Switzerland: International Union for Conservation of Nature. http://afrotheria.net/.
2. Barnes BM. Freeze avoidance in a mammal: body temperatures below 0°C in an arctic hibernator. *Science* 244: 1593–1595, 1989.
3. Barnes BM, Ritter D. Patterns of body temperature changes in hibernating arctic ground squirrels In: *Life in the Cold* edited by Carey C, Florant G, Wunder B, Horwitz B. Boulder, CO: Westview Press, 1993 p. 119–130.
4. Berger RJ. Slow wave sleep, shallow torpor and hibernation: homologous states of diminished metabolism and body temperature. *Biol Psychol* 19: 305–326, 1984.
5. Berriel Diaz M, Lange M, Heldmaier G, Klingenspor M. Depression of transcription and translation during daily torpor in the Djungarian hamster (*Phodopus sungorus*). *J Comp Physiol B* 174: 495–502, 2004.
6. Bouma HR, Kroese FGM, Kok JW, Talaei F, Boerema AS, Herwig A, Draghiciu O, van Buiten A, Epema AH, van Dam A, Strijkstra AM, Henning RH. Low body temperature governs the decline of circulating lymphocytes during hibernation through sphingosine-1-phosphate. *Proc Natl Acad Sci USA* 108: 2052–2057, 2011.
7. Boyles JG, Thompson AB, McKechnie AE, Malan E, Humphries MM, Careau V. A global heterothermic continuum in mammals. *Global Ecol Biogeogr* 22: 1029–1039, 2013.
8. Brown DC, Mulhausen RO, Andrew DJ, Seal US. Renal function in anesthetized dormant and active bears. *Am J Physiol* 220: 293–298, 1971.
9. Brown DJA, Brugger H, Boyd J, Paal P. Accidental hypothermia. *N Engl J Med* 367: 1930–1938, 2012.
10. Buck CL, Barnes BM. Effects of ambient temperature on metabolic rate, respiratory quotient, and torpor in an arctic hibernator. *Am J Physiol Regul Integr Comp Physiol* 279: R255–R262, 2000.
11. Cajochen C, Kräuchi K, Wirz-Justice A. Role of melatonin in the regulation of human circadian rhythms and sleep. *J Neuroendocrinol* 15: 432–437, 2003.
12. Carey HV, Andrews MT, Martin SL. Mammalian hibernation: cellular and molecular responses to depressed metabolism and low temperature. *Physiol Rev* 83: 1153–1181, 2003.
13. Dausmann KH, Glos J, Ganzhorn JU, Heldmaier G. Hibernation in the tropics: lessons from a primate. *J Comp Physiol B* 175: 147–155, 2005.
14. Dausmann KH, Glos J, Ganzhorn JU, Heldmaier G. Physiology: hibernation in a tropical primate. *Nature* 429: 825–826, 2004.
15. Dausmann KH, Glos J, Heldmaier G. Energetics of tropical hibernation. *J Comp Physiol B* 179: 345–357, 2009.
16. Eckel-Mahan K, Sassone-Corsi P. Metabolism and the circadian clock converge. *Physiol Rev* 93: 107–135, 2013.
17. Epperson LE, Karimpour-Fard A, Hunter LE, Martin SL. Metabolic cycles in a circannual hibernator. *Physiol Genomics* 43: 799–807, 2011.
18. Fedorov VB, Goropashnaya AV, Toien O, Stewart NC, Chang C, Wang H, Yan J, Showe LC, Showe MK, Barnes BM. Modulation of gene expression in heart and liver of hibernating black bears (*Ursus americanus*). *BMC Genomics* 12: 171, 2011.
19. Fedorov VB, Goropashnaya AV, Toien O, Stewart NC, Gracey AY, Chang C, Qin S, Pertea G, Quackenbush J, Showe LC, Showe MK, Boyer BB, Barnes BM. Elevated expression of protein biosynthesis genes in liver and muscle of hibernating black bears (*Ursus americanus*). *Physiol Genomics* 37: 108–118, 2009.
20. Garbutt N. *Mammals of Madagascar: A Complete Guide*. New Haven, CT: Yale Univ. Press, 2007.
21. Geiser F. Hibernation. *Curr Biol* 23: R188–R193, 2013.
22. Geiser F. Metabolic rate and body temperature reduction during hibernation and daily torpor. *Annu Rev Physiol* 66: 239–274, 2004.
23. Geiser F, Hiebert S, Kenagy GJ. Torpor bout duration during the hibernation season of two sciurid rodents: interrelations with temperature and metabolism. *Physiol Zool* 63: 489–503, 1990.
24. Geiser F, Martin G. Torpor in the Patagonian opossum (*Lestodelphys halli*): implications for the evolution of daily torpor and hibernation. *Naturwissenschaften* 100: 975–981, 2013.
25. Grabek KR, Diniz Behn C, Barsh GS, Hesselberth JR, Martin SL. Enhanced stability and polyadenylation of select mRNAs support rapid thermogenesis in the brown fat of a hibernator. *Elife*. In press.
26. Grabek KR, Karimpour-Fard A, Epperson LE, Hindle AG, Hunter LE, Martin SL. Multistate proteomics analysis reveals novel strategies used by a hibernator to precondition the heart and conserve ATP for winter heterothermy. *Physiol Genomics* 43: 1263–1275, 2011.
27. Grabek KR, Martin SL, Hindle AG. Proteomics approaches shed new light on hibernation physiology. *J Comp Physiol B*. In press.

28. Hampton M, Melvin RG, Andrews MT. Transcriptomic analysis of brown adipose tissue across the physiological extremes of natural hibernation. *PLos One* 8: e85157, 2013.

29. Heller HC. Hibernation: neural aspects. *Ann Rev Physiol* 41: 305–321, 1979.

30. Heller HC, Ruby NF. Sleep and circadian rhythms in mammalian torpor. *Annu Rev Physiol* 66: 275–289, 2004.

31. Hellgren EC. Physiology of hibernation in bears. *Ursus* 10: 467–477, 1998.

32. Hindle AG, Grabek KR, Epperson LE, Karimpour-Fard A, Martin SL. Metabolic changes associated with the long winter fast dominate the liver proteome in hibernating ground squirrels. *Physiol Genomics* 46: 348–361, 2014.

33. Hindle AG, Karimpour-Fard A, Epperson LE, Hunter LE, Martin SL. Skeletal muscle proteomics: carbohydrate metabolism oscillates with seasonal and torpor-arousal physiology of hibernation. *Am J Physiol Regul Integr Comp Physiol* 301: R1440–R1452, 2011.

34. Hindle AG, Martin SL. Cytoskeletal regulation dominates temperature-sensitive proteomic changes of hibernation in forebrain of 13-lined ground squirrels. *PLos One* 8: e71627, 2013.

35. Hindle AG, Martin SL. Intrinsic circannual regulation of brown adipose tissue form and function in tune with hibernation. *Am J Physiol Endocrinol Metab* 306: E284–E299, 2014.

36. Hindle AG, Otis JP, Epperson LE, Hornberger TA, Goodman CA, Carey HV, Martin SL. Prioritization of skeletal muscle regrowth for emergence from hibernation. *J Exp Biol* 218: 276–284, 2015.

37. Huang Y, Ainsley JA, Reijmers LG, Jackson FR. Translational profiling of clock cells reveals circadianly synchronized protein synthesis. *PLoS Biol* 11: e1001703, 2013.

38. Jani A, Martin SL, Jain S, Keys D, Edelstein CL. Renal adaptation during hibernation. *Am J Physiol Renal Physiol* 305: F1521–F1532, 2013.

39. Jani A, Orlicky DJ, Karimpour-Fard A, Epperson LE, Russell RL, Hunter LE, Martin SL. Kidney proteome changes provide evidence for a dynamic metabolism and regional redistribution of plasma proteins during torpor-arousal cycles of hibernation. *Physiol Genomics* 44: 717–727, 2012.

40. Jinka TR, Rasley BT, Drew KL. Inhibition of NMDA-type glutamate receptors induces arousal from torpor in hibernating arctic ground squirrels (*Urocitellus parryii*). *J Neurochem* 122: 934–940, 2012.

41. Jinka TR, Toien O, Drew KL. Season primes the brain in an arctic hibernator to facilitate entrance into torpor mediated by adenosine A1 receptors. *J Neurosci* 31: 10752–10758, 2011.

42. Ko CH, Takahashi JS. Molecular components of the mammalian circadian clock. *Hum Mol Genet* 15: R271–R277, 2006.

43. Kobbe S, Dausmann K. Hibernation in Malagasy mouse lemurs as a strategy to counter environmental challenge. *Naturwissenschaften* 96: 1221–1227, 2009.

44. Kobbe S, Ganzhorn J, Dausmann K. Extreme individual flexibility of heterothermy in free-ranging Malagasy mouse lemurs (*Microcebus griseorufus*). *J Comp Physiol B* 181: 165–173, 2011.

45. Kojima S, Sher-Chen EL, Green CB. Circadian control of mRNA polyadenylation dynamics regulates rhythmic protein expression. *Genes Dev* 26: 2724–2736, 2012.

46. Lakin-Thomas PL. Transcriptional feedback oscillators: maybe, maybe not. *J Biol Rhythms* 21: 83–92, 2006.

47. Levesque DL, Lovasoa OMA, Rakotoharimalala SN, Lovegrove BG. High mortality and annual fecundity in a free-ranging basal placental mammal, Setifer setosus (Tenrecidae: Afrosoricida). *J Zool Lond* 291: 205–212, 2013.

48. Liu Y, Hu W, Murakawa Y, Yin J, Wang G, Landthaler M, Yan J. Cold-induced RNA-binding proteins regulate circadian gene expression by controlling alternative polyadenylation. *Sci Rep* 3: 2054, 2013.

49. Lovegrove B, Génin F. Torpor and hibernation in a basal placental mammal, the Lesser Hedgehog Tenrec *Echinops telfairi*. *J Comp Physiol B* 178: 691–698, 2008.

50. Lovegrove BG. The evolution of endothermy in Cenozoic mammals: a plesiomorphic-apomorphic continuum. *Biol Rev* 87: 128–162, 2012.

51. Lovegrove BG, Canale C, Levesque D, Fluch G, Ř̆eháková-Petrů M, Ruf T. Are tropical small mammals physiologically vulnerable to arrhenius effects and climate change? *Physiol Biochem Zool* 87: 30–45, 2014.

52. Lovegrove BG, Lobban KD, Levesque DL. Mammal survival at the Cretaceous-Palaeogene boundary: metabolic homeostasis in prolonged tropical hibernation in tenrecs. *Proc Biol Sci* 281: 20141304, 2014.

53. Lovegrove G, Kortner G, Geiser F. The energetic cost of arousal from torpor in the marsupial *Sminthopsis macroura*: benefits of summer ambient temperature cycles. *J Comp Physiol B* 169: 11–18, 1999.

54. Lyman CP, Willis JS, Malan A, Wang LCH. *Hibernation and Torpor in Mammals and Birds*. New York: Academic, 1982.

55. Malan A. Is the torpor-arousal cycle of hibernation controlled by a non-temperature-compensated circadian clock? *J Biol Rhythms* 25: 166–175, 2010.

56. Morin P Jr, Storey KB. Mammalian hibernation: differential gene expression and novel application of epigenetic controls. *Int J Dev Biol* 53: 433–442, 2009.

57. Mzilikazi N, Lovegrove BG, Ribble DO. Exogenous passive heating during torpor arousal in free-ranging rock elephant shrews, *Elephantulus myurus*. *Oecologia (Berl)* 133: 307–314, 2002.

58. Nelson CJ, Otis JP, Carey HV. Global analysis of circulating metabolites in hibernating ground squirrels. *Comp Biochem Physiol Part D Genomics Proteomics* 5: 265–273, 2010.

59. Nelson CJ, Otis JP, Martin SL, Carey HV. Analysis of the hibernation cycle using LC-MS based metabolomics in ground squirrel liver. *Physiol Genomics* 37: 43–51, 2009.

60. Nelson RA, Wahner HW, Jones JD, Ellefson RD, Zollman PE. Metabolism of bears before, during, and after winter sleep. *Am J Physiol* 224: 491–496, 1973.

61. O'Leary MA, Bloch JI, Flynn JJ, Gaudin TJ, Giallombardo A, Giannini NP, Goldberg SL, Kraatz BP, Luo ZX, Meng J, Ni X, Novacek MJ, Perini FA, Randall ZS, Rougier GW, Sargis EJ, Silcox MT, Simmons NB, Spaulding M, Velazco PM, Weksler M, Wible JR, Cirranello AL. The placental mammal ancestor and the post-K-Pg radiation of placentals. *Science* 339: 662–667, 2013.

62. Osborne PG, Gao B, Hashimoto M. Determination in vivo of newly synthesized gene expression in hamsters during phases of the hibernation cycle. *Jpn J Physiol* 54: 295–305, 2004.

63. Pan P, van Breukelen F. Preference of IRES-mediated initiation of translation during hibernation in golden-mantled ground squirrels, *Spermophilus lateralis*. *Am J Physiol Regul Integr Comp Physiol* 301: R370–R377, 2011.

64. Reddy AB, Rey G. Metabolic and nontranscriptional circadian clocks: eukaryotes. *Ann Rev Biochem* 83: 165–189, 2014.

65. Revel FG, Herwig A, Garidou ML, Dardente H, Menet JS, Masson-Pévet M, Simonneaux V, Saboureau M, Pévet P. The circadian clock stops ticking during deep hibernation in the European hamster. *Proc Natl Acad Sci USA* 104: 13816–13820, 2007.

66. Rey G, Reddy AB. Connecting cellular metabolism to circadian clocks. *Trends Cell Biol* 23: 234–241, 2013.

67. Robles MS, Cox J, Mann M. In-vivo quantitative proteomics reveals a key contribution of post-transcriptional mechanisms to the circadian regulation of liver metabolism. *PLos Genet* 10: e1004047, 2014.

68. Romiguier J, Ranwez V, Delsuc F, Galtier N, Douzery EJP. Less is more in mammalian phylogenomics: AT-rich genes minimize tree conflicts and unravel the root of placental mammals. *Mol Biol Evol* 30: 2134–2144, 2013.

69. Ruediger J, Van der Zee EA, Strijkstra AM, Aschoff A, Daan S, Hut RA. Dynamics in the ultrastructure of asymmetric axospinous synapses in the frontal cortex of hibernating European ground squirrels (*Spermophilus citellus*). *Synapse* 61: 343–352, 2007.

70. Ruf T, Geiser F. Daily torpor and hibernation in birds and mammals. *Biol Rev*. In press.

71. Russell RL, O'Neill PH, Epperson LE, Martin SL. Extensive use of torpor in 13-lined ground squirrels in the fall prior to cold exposure. *J Comp Physiol B* 180: 1165–1172, 2010.

72. Sancar G, Sancar C, Brunner M. Metabolic compensation of the Neurospora clock by a glucose-dependent feedback of the circadian repressor CSP1 on the core oscillator. *Genes Dev* 26: 2435–2442, 2012.

73. Schwartz C, Hampton M, Andrews MT. Seasonal and regional differences in gene expression in the brain of a hibernating mammal. *PLos One* 8: e58427, 2013.

74. Serkova NJ, Rose JC, Epperson LE, Carey HV, Martin SL. 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, 2007.

75. Stangherlin A, Reddy AB. Regulation of circadian clocks by redox homeostasis. *J Biol Chem* 288: 26505–26511, 2013.

76. Tøien Ø, Blake J, Edgar DM, Grahn DA, Heller HC, Barnes BM. Hibernation in black bears: independence of metabolic suppression from body temperature. *Science* 331: 906–909, 2011.

77. Tu BP, McKnight SL. Metabolic cycles as an underlying basis of biological oscillations. *Nat Rev Mol Cell Biol* 7: 696–701, 2006.

78. Tu BP, Mohler RE, Liu JC, Dombek KM, Young ET, Synovec RE, McKnight SL. Cyclic changes in metabolic state during the life of a yeast cell. *Proc Natl Acad Sci USA* 104: 16886–16891, 2007.

79. Turbill C, Bieber C, Ruf T. Hibernation is associated with increased survival and the evolution of slow life histories among mammals. *Proc Biol Sci* 278: 3355–3363, 2011.

80. van Breukelen F, Martin SL. Molecular adaptations in mammalian hibernators: unique adaptations or generalized responses? *J Appl Physiol* 92: 2640–2647, 2002.

81. van Breukelen F, Martin SL. Reversible depression of transcription during hibernation. *J Comp Physiol B* 172: 355–361, 2002.

82. van Breukelen F, Martin SL. Translational initiation is uncoupled from elongation at 18°C during mammalian hibernation. *Am J Physiol Regul Integr Comp Physiol* 281: R1374–R1379, 2001.

83. Velickovska V, Lloyd BP, Qureshi S, van Breukelen F. Proteolysis is depressed during torpor in hibernators at the level of the 20S core protease. *J Comp Physiol B* 175: 329–335, 2005.

84. Vermillion KL, Anderson KJ, Hampton M, Andrews MT. Gene expression changes controlling distinct adaptations in the heart and skeletal muscle of a hibernating mammal. *Physiol Genomics* 47: 58–74, 2015.

85. Vogt FD, Lynch GR. Influence of ambient temperature, nest availability, huddling, and daily torpor on energy expenditure in the white-footed mouse *Peromyscus leucopus*. *Physiol Zool* 55: 56–63, 1982.

86. von der Ohe CG, Darian-Smith C, Garner CC, Heller HC. Ubiquitous and temperature-dependent neural plasticity in hibernators. *J Neurosci* 26: 10590–10598, 2006.

87. von der Ohe CG, Garner CC, Darian-Smith C, Heller HC. Synaptic protein dynamics in hibernation. *J Neurosci* 27: 84–92, 2007.

88. Wang LCH. Time patterns and metabolic rates of natural torpor in the Richardson's ground squirrel. *Can J Zool* 57: 149–155, 1979.

89. Willem J Hillenius, John A. Ruben the evolution of endothermy in terrestrial vertebrates: Who? When? Why? *Physiol Biochem Zool* 77: 1019–1042, 2004.

90. Williams CT, Barnes BM, Buck CL. Daily body temperature rhythms persist under the midnight sun but are absent during hibernation in free-living arctic ground squirrels. *Biol Lett* 8: 31–34, 2012.

91. Williams CT, Barnes BM, Buck CL. Persistence, entrainment, and function of circadian rhythms in polar vertebrates. *Physiology* 30: 86–96, 2015.

92. Williams CT, Barnes BM, Richter M, Buck CL. Hibernation and circadian rhythms of body temperature in free-living Arctic ground squirrels. *Physiol Biochem Zool* 85: 397–404, 2012.

93. Wilz M, Heldmaier G. Comparison of hibernation, estivation and daily torpor in the edible dormouse, Glis glis. *J Comp Physiol B* 170: 511–521, 2000.

94. Yan J, Barnes BM, Kohl F, Marr TG. Modulation of gene expression in hibernating arctic ground squirrels. *Physiol Genomics* 32: 170–181, 2008.

95. Zepelin H, Rechtschaffen A. Mammalian sleep, longevity, and energy metabolism. *Brain Behav Evol* 10: 425–470, 1974.

96. Zervanos SM, Maher CR, Florant GL. Effect of body mass on hibernation strategies of woodchucks (*Marmota monax*). *Integr Comp Biol* 54: 443–451, 2014.

97. Zervanos SM, Maher CR, Waldvogel JA, Florant GL. Latitudinal differences in the hibernation characteristics of woodchucks (*Marmota monax*). *Physiol Biochem Zool* 83: 135–141, 2010.