

The Origin of Mammalian Heterothermy: A Case for Perpetual Youth?

MICHAEL B. HARRIS,¹ LINK E. OLSON,^{1,2} AND WILLIAM K. MILSOM³

¹ Institute of Arctic Biology, University of Alaska Fairbanks, Fairbanks, Alaska, USA

² University of Alaska Museum, Fairbanks, Alaska, USA

³ Department of Zoology, University of British Columbia, Vancouver, BC, Canada

The phylogenetic distribution of heterothermic mammals is diverse, encompassing several independent lineages in which many heterotherms are closely related to nonheterotherms and in which there is no identifiable heterothermic common ancestor (Cade, 1964; Lyman, 1982; Nedergaard and Cannon, 1990; Malan, 1996; Geiser, 1998). The ability to utilize heterothermy, however, depends on a host of physiological specializations that appear common to all species that employ this strategy. The breadth and complexity of specializations underlying the phenotype, and the conservation of these specializations between species, argues against a polyphyletic origin for heterothermy and suggests that a capacity for heterothermy is a retained ancestral trait (Cade, 1964; Malan, 1996; Geiser, 1998).

It had been proposed that heterothermy represented an ancient characteristic found only in “primitive” mammals (Cade, 1964). The distribution of heterothermy, however, is not restricted to taxa traditionally considered “primitive” and includes placental mammals as well as marsupials and monotremes (Cade, 1964; Lyman, 1982; Nedergaard and Cannon, 1990; Malan, 1996; Geiser, 1998; Carey et al., 2003). One recent theory suggests that the physiological changes associated with sleep, which are common to all mammals, have been acted upon and extended in a polyphyletic fashion to produce the physiological changes associated with heterothermy (Berger, 1984; Kilduff et al., 1993).

Life in the Cold: Evolution, Mechanisms, Adaptation, and Application. Twelfth International Hibernation Symposium. Biological Papers of the University of Alaska, number 27. Institute of Arctic Biology, University of Alaska Fairbanks, Alaska, USA.

Although an intriguing hypothesis, many characteristics shared by mammalian heterotherms are not related to sleep physiology.

However, remarkable similarity is apparent between the physiological characteristics associated with heterothermy and those associated with another common “ancestral trait,” neonatal life. In this article we argue that the capacity for heterothermy in adult mammals may have arisen multiple times in unrelated species through retention of heterothermic characteristics common to neonatal mammals: an example of evolutionary adaptation by neoteny. Heterothermy in adult mammals could be a paedomorphic trait, resulting from the retention of juvenile characteristics into adult life.

Although the ability to hibernate appears to involve unique patterns of gene expression, the phenotype has not been associated with novel genes (Srere et al., 1992; Carey et al., 2003). It would appear that the genes required to specify the hibernation phenotype are common to the mammalian genome. The hypothesis of “hibernator as neonate” would suggest that the genetic potential for heterothermy is expressed to some extent in all neonates and that heterothermy in adults results from the continued expression of such genes. This could even reflect the genetic potential to accommodate heterothermy in reptiles, conserved in the mammalian genome (Malan, 1996; Geiser, 1998).

We propose that in species where the adaptive benefits of heterothermy persisted beyond the neonatal period, this trait was retained into adulthood. This resulted in the continued expression of genes and gene products advantageous to the neonate for facilitating heterothermy in adults. Variations in the conserved expression of this potential provide the basis for the range of heterothermic phenotypes spanning from facultative torpor to shallow and deep torpor and seasonal hibernation.

In support of this hypothesis are the profound similarities between many general physiological characteristics of neonates and specific “adaptations” of heterothermic mammals. The following represent examples, taken from a range of systems, intended to illustrate the diversity of adaptations common to heterothermic mammals that could have originated from neonatal physiology.

Reduced Body Temperature and Metabolic Suppression

Most neonatal mammals can tolerate extreme reductions in body temperature compared to their adult counterparts (Guignard and Gillieron, 1997). This goes beyond mere tolerance, however, and orchestrated reductions in metabolism and body temperature are relatively common neonatal traits. Thus, endogenous

torpor-like variations in core temperature and metabolism are well documented in many neonatal rodents (Nuesslein-Hildesheim et al., 1995).

Tolerance to Hypoxia, Ischemia, and Asphyxia

During hibernation and torpor, heterothermic mammals appear to suffer no ill effects from prolonged hypoxia, asphyxia, or ischemia. This is also true of euthermic heterotherms, and isolated tissues from heterotherms, but not of mature nonheterotherms or their tissues (Frerichs and Hallenbeck, 1998, see Drew et al., 2004, for review). Such tolerance is also seen in mammalian neonates, but is not retained in adults of nonheterotherms (Frerichs, 1999; Singer, 1999; Wagner et al., 1999; Zhou et al. 2001; Drew et al., 2004).

Brown Adipose Tissues (BAT)

BAT is essential for nonshivering thermogenesis and rapid warming during arousal from torpor in heterothermic placental mammals. Pronounced BAT deposits are so universal and conserved in heterothermic placental mammals that they have been considered a deterministic feature described as a “hibernation gland” (Cade, 1964). Similar pronounced BAT deposits serve the same role in rapid thermogenesis in mammalian neonates. In most nonheterothermic mammals BAT is greatly reduced or lost during maturation. Incidentally, although heterothermy occurs both in mammals and birds, homology between the two has been questioned because of the absence of BAT in birds (discussed in Geiser, 1998; Geiser and Ruf, 1995). Heterothermy in birds and mammals may yet be homologous, however, if it developed through the retention of the heterothermic capacity shared by the neonates of each group, with the independent origin of BAT in neonatal placental mammals and not in neonatal birds. The limited role of BAT in heterothermic monotremes and marsupials may be similarly explained.

White Adipose Tissues, Fat Metabolism, and Lipogenesis

The metabolism of the mammalian neonate is acutely refined to convert a high-fat diet into white adipose tissue, and nonheterotherms generally show age-related decreases in this capacity for lipogenesis. Seasonal hibernators, however, maintain the ability to build fat rapidly in the fall and, in species that do not store food, to fuel metabolism primarily from stored fat during hibernation (Nedergaard and Cannon, 1990; Carey et al., 2003).

Digestive System Plasticity

During the postnatal period mammals switch from a prenatal strategy, where nutrients are supplied to the fetal blood via the umbilical circulation, to autonomous nutrient uptake requiring ingestion, digestion, and absorption of nutrients across the gut epithelium. This switch necessitates rapid growth in the neonatal digestive system. During prolonged torpor, the digestive system atrophies, and is rapidly rebuilt on arousal (Carey, 1990). This rapid regrowth of the digestive system could reflect processes similar to those occurring in the neonate.

Autonomic Nervous System

Cardiac Sympathetic Innervation

The heart is influenced by both sympathetic and parasympathetic branches of the autonomic nervous system. Parasympathetic innervation is established *in utero*, while cardiac sympathetic innervation develops during the neonatal period in most mammals (Kralios and Kralios, 1996; Johansson, 1996; Wang and Zhou, 1999). Cardiac sympathetic innervation appears to be diminished or absent in mammalian hibernators (Neilsen and Owman, 1968). In both cases, this is proposed to be an adaptation designed to limit cardiac fibrillation.

Vagal Afferent Integration

Breathing is generated by the brainstem but is shaped by respiratory reflexes involving feedback from a host of receptors, including afferent projections of the vagus nerve responding to lung stretch. The magnitude of many such reflexes decrease with age. When euthermic, however, some heterothermic rodents demonstrate an acute reliance on vagal feedback unlike other mature mammals but similar to the situation observed in neonates (Fedorko et al., 1988; Harris and Milsom, 2001).

Neuronal Growth and Plasticity

Heterotherms demonstrate distinct reductions in the complexity of synapses during torpor and remarkable synaptic expansion on arousal (Popov et al., 1992). Heterotherms also demonstrate greater tolerances to and recovery from brain injury (reviewed in Zhou et al., 2001). These are traits that strongly mimic the neural plasticity of the neonatal period.

Pulmonary Surfactant

Surfactant controls the surface tension of the fluid lining the lung. Homeothermic mammals experience pulmonary surfactant dysfunction with relatively small fluctuations in body temperature, while the surfactant systems of neonates and heterotherms function over a wide range of temperatures (Ormond et al., 2003; Slocombe et al., 2000). Surfactant composition changes during postnatal development and in heterotherms in and out of torpor (Ballard et al., 2003; Slocombe et al., 2000).

Haemoglobin

The oxygen-carrying capacity of the blood of heterotherms is enhanced relative to that of nonheterotherms (Maginniss and Milsom, 1994). Furthermore, in heterotherms, the oxygen affinity of the oxygen-binding protein haemoglobin is greater than that found in nonheterotherm haemoglobins. Haemoglobin is also different in the fetus and the adult, with fetal haemoglobin having a higher affinity for oxygen. Postnatal maturation is associated with a gradual replacement of fetal haemoglobin with the lower affinity, adult form (Halleux et al., 2002).

An Example from the Tenrecidae

Much of the theory surrounding the origins of mammalian heterothermy has dealt with a limited subset of living mammals. Most data come from rodents, marsupials, and monotremes (Cade, 1964; Lyman, 1982; Nedergaard and Cannon, 1990; Malan, 1996; Geiser, 1998; Carey et al., 2003). Identifying closely related heterothermic and nonheterothermic species with which to test theories of the origins of heterothermy is difficult. Here we provide such an example, in a group that has thus far received relatively little attention from the physiological community. The mammalian family Tenrecidae includes three species restricted to equatorial Africa and 26 currently recognized species on the island of Madagascar (Jenkins, in press). The Malagasy tenrecs represent a spectacular example of an island radiation resulting from a single colonizing common ancestor (Olson and Goodman, 2003). In addition to the striking level of interspecific variation in morphology, ecology, life history, and behavior found in Malagasy tenrecs (reviewed in Olson, 1999, and Olson and Goodman, 2003), there is a range of homeothermic capacities across the clade (reviewed in Racey and Stephenson, 1996). This range includes species that fail to show homeothermy at any temperature (*Geogale aurita*), others that utilize daily or seasonal torpor (*Tenrec ecaudatus*, *Hemicentetes nigriceps*, *H. semispinosus*) and still oth-

ers that maintain relatively constant body temperatures (*Microgale cowani*, *M. melanorrhachis*) (Stephenson, 1991; Racey and Stephenson, 1996). Of particular interest in the current context are the spiny tenrecs (subfamily Tenrecinae). Molecular and morphological data strongly support a sister relationship between two species in this five-member clade, the lesser (*Echinops telfairi*) and greater (*Setifer setosus*) Malagasy hedgehog tenrecs. While *Echinops* and *Setifer* are very similar externally, subtle morphological differences between the two (reviewed in Olson, 1999) suggest that several features in *Echinops* may be paedomorphic (neotenus) relative to its closest living relative, *Setifer*. These features include differences in body size—adults of *Setifer* tend to be much larger than those of *Echinops* (Garbutt, 1999)—and, in *Echinops*, a failure to develop a third molar (Thomas, 1892). *Echinops* is the only member of the family that lacks this tooth, which is the last of the three molars to erupt in all other species.

Physiologically, *Echinops* is striking in its inability to maintain a constant body temperature (T_b) across a broad range of ambient temperatures (T_a) (Nicoll and Thompson, 1987; reviewed in Stephenson, 1991) and is considered to be a true heterotherm except during periods of gestation and lactation (see Poppitt et al., 1994). Field and captive studies on *Setifer*, on the other hand, have demonstrated its ability to maintain a T_b higher than T_a throughout its annual cycle (Eisenberg and Gould, 1970) and, thus, *Setifer* is classified as being more homeothermic than *Echinops*. Both species are known to enter daily and seasonal torpor, but torpor in *Setifer* is believed to be less profound than in *Echinops*. (Eisenberg and Gould, 1970; Stephenson, 1991; Salton and Buffenstein, 2004).

While we would clearly not want to base our hypothesis on a single empirical example, we offer the case of *Echinops* and *Setifer* as evidence of a possible relationship between paedomorphosis and relative heterothermy.

Conclusion

There is remarkable similarity between traits underlying the heterothermic phenotype and traits common to neonatal mammals. Thus, we propose that mammalian heterothermy is an example of evolution through neoteny and that the seemingly polyphyletic distribution of heterothermy in mammals (and perhaps also birds) results from independent cases of arrested physiological development in lineages where the preservation of heterothermic capacity in adults conveyed a selective advantage. The conservation of complex traits in distantly related heterotherms reflects a common origin in neonatal physiology. This theory provides a basis for testable hypotheses, and would predict trait similarities between

neonates of heterothermic and nonheterothermic sister species, and a retention of traits during maturation in heterotherms but a loss in nonheterotherms. This theory also predicts that when one species is more heterothermic with respect to its sister species, it will also be relatively paedomorphic. Answers to previously enigmatic questions pertaining to adaptations for torpor and hibernation could be sought through comparison with neonates. Similarly, insights into neonatal physiology and certain pathophysiologicals might be gained through investigation of heterothermic mammals.

References

- Ballard PL, Merrill JD, Godinez RI, Godinez MH, Truog WE, Ballard RA (2003) Surfactant protein profile of pulmonary surfactant in premature infants. *Am J Respir Crit Care Med* 168(9):1123–8.
- Berger RJ (1984) Slow wave sleep, shallow torpor, and hibernation: Homologous states of diminished metabolism and body temperature. *Biol Psychol* 19(3–4): 305–26.
- Cade TJ (1964) The evolution of torpidity in rodents. *Annales Academiae Scientiarum Fennicae, A: IV. Biologica* 71(6):78–112.
- Carey HV (1990) Seasonal changes in mucosal structure and function in ground squirrel intestine. *Am J Physiol Regul Integr Comp Physiol* 259:R385–R392.
- Carey HV, Andrews MT, Martin SL (2003) Mammalian hibernation: Cellular and molecular responses to depressed metabolism and low temperature. *Physiol Rev* 83(4):1153–81.
- Drew KL, Harris MB, LaManna JC, Smith MA, Zhu XW, Ma YL (in press) Hypoxia Tolerance in Mammalian Heterotherms. *J Exp Biol*.
- Eisenberg JF, Gould E (1970) *The Tenrecs: A Study in Mammalian Behavior and Evolution*. Washington, DC: Smithsonian Institution Press.
- Fedorko L, Kelly EN, England SJ (1988). Importance of vagal afferents in determining ventilation in newborn rats. *J Appl Physiol* 65:1033–1039.
- Frerichs KU (1999) Neuroprotective strategies in nature—Novel clues for the treatment of stroke and trauma. *Acta Neurochir Suppl (Wien)* 73:57–61.
- Frerichs KU, Hallenbeck JM (1998) Hibernation in ground squirrels induces state and species-specific tolerance to hypoxia and aglycemia: An *in vitro* study in hippocampal slices. *J Cereb Blood Flow Metab* 18:168–175.
- Garbutt, N. 1999. *Mammals of Madagascar*. Sussex: Pica Press.

- Geiser F, Ruf T (1995) Hibernation versus daily torpor in mammals and birds: Physiological variables and classification of torpor patterns. *Physiol Zool* 68: 935–966.
- Geiser F (1998) Evolution of daily torpor and hibernation in birds and mammals: importance of body size. *Clin Exp Pharmacol Physiol* 25(9):736–9.
- Guignard JP, Gillieron P (1997) Effect of modest hypothermia on the immature kidney. *Acta Paediatr* 86:1040–1.
- Halleux V, De., Truttman A, Gagnon C, Bard H (2002) The effect of blood transfusion on the hemoglobin oxygen dissociation curve of very early preterm infants during the first week of life. *Semin Perinatol* 26(6):411–5.
- Harris MB, Milsom WK (2001) Vagal feedback is essential for breathing in unanesthetized ground squirrels. *Respir Physiol* 125(3):199–212.
- Jenkins PD (in press). Family Tenrecidae. In Wilson DE, Reeder DM (eds), *Mammal Species of the World: A Taxonomic and Geographic Reference*. Washington, DC: Smithsonian Institution Press.
- Johansson BW (1996) The hibernator heart: Nature's model of resistance to ventricular fibrillation. *Cardiovasc Res* 31(5):826–32.
- Kilduff TS, Krilowicz B, Milsom WK, Trachsel L, Wang LC (1993) Sleep and mammalian hibernation: Homologous adaptations and homologous processes? *Sleep* 16(4):372–86.
- Kralios FA, Kralios AC (1996) Ventricular fibrillation in the neonate: Elusive or illusive? *Reprod Fertil Dev* 8(1):49–60.
- Lyman CP (1982) Who is among the hibernators. In Lyman Willis, Malan and Wang (eds), *Hibernation and Torpor in Mammals and Birds*. New York: Academic Press, pp. 12–36.
- Maginniss LA, Milsom WK. (1994) Effects of hibernation on blood oxygen transport in the golden-mantled ground squirrel. *Respir Physiol* 95(2):195–208.
- Malan A (1996) The origins of hibernation: A reappraisal. In Geiser F, Hulbert AJ, Nicol SC (eds), *Adaptations to the Cold: Tenth International Hibernation Symposium*. Armidale: University of New England Press. Pp. 1–6.
- Nedergaard J, Cannon B (1990) Mammalian hibernation. *Philos Trans R Soc Lond B Biol Sci.* 326(1237):669–86.
- Neilsen KC, Owman CH (1968) Differences in cardiac adrenergic innervation between hibernators and nonhibernating mammals. *Acta Physiol Scand* 74(sup 316):1–30.

- Nicoll, ME, Thompson SD (1987). Basal metabolic rates and energetics of reproduction in therian mammals: Marsupials and placentals compared. *Symp Zool Soc Lond* 57:7–27.
- Nuesslein-Hildesheim B, Imai-Matsumura K, Doring H, Schmidt I (1995) Pronounced juvenile circadian core temperature rhythms exist in several strains of rats but not in rabbits. *J Comp Physiol [B]* 165(1):13–7.
- Ormond CJ, Orgeig S, Daniels CB, Milsom WK (2003) Thermal acclimation of surfactant secretion and its regulation by adrenergic and cholinergic agonists in type II cells isolated from warm-active and torpid golden-mantled ground squirrels, *Spermophilus lateralis*. *J Exp Biol* 206:3031–41.
- Olson LE (1999) Systematics, Evolution, and Biogeography of Madagascar's Tenrecs (Mammalia: Tenrecidae). Unpublished PhD dissertation. University of Chicago, Chicago, IL.
- Olson LE, Goodman SM (2003). Phylogeny of Madagascar's tenrecs (Lipotyphla, Tenrecidae). In Benstead G (ed), *Natural History of Madagascar*, Chicago: University of Chicago Press. Pp. 1235–1242.
- Popov VI, Bocharova LS, Bragin AG (1992) Repeated changes of dendritic morphology in the hippocampus of ground squirrels in the course of hibernation. *Neuroscience* 48:45–51.
- Poppitt, SD, Speakman JR, Racey PA (1994) Energetics of reproduction in the lesser hedgehog tenrec, *Echinops telfairi* (Martin). *Physiol Zool* 67:976–994.
- Racey PA, Stephenson PJ (1996) Reproductive and energetic differentiation of the Tenrecidae of Madagascar. In Lourenço (ed), *Biogéographie de Madagascar*. Paris: ORSTROM. Pp. 307–320
- Salton J, Buffenstein R (2004) Field thermoregulatory profiles in tenrecs from the rainforest and dry forest of Madagascar. *Int Comp Biol* 43(6).
- Singer D (1999) Neonatal tolerance to hypoxia: A comparative-physiological approach. *Comp Biochem Physiol A Mol Integr Physiol* 123(3):221–34.
- Slocombe NC, Codd JR, Wood PG, Orgeig S, Daniels CB (2000) The effect of alterations in activity and body temperature on the pulmonary surfactant system in the lesser long-eared bat *Nyctophilus geoffroyi*. *J Exp Biol* 16:2429–35.
- Srere HK, Wang LC, Martin SL (1992) Central role for differential gene expression in mammalian hibernation. *Proc Natl Acad Sci USA* 89(15):7119–23.
- Stephenson PJ (1991) Reproductive energetics of the Tenrecidae (Mammalia: Insectivora). Unpublished PhD dissertation. Aberdeen, UK: University of Aberdeen.

- Thomas O (1892). On the insectivorous genus *Echinops*, Martin, with notes on the dentition of the allied genera. *Proceedings of the Zoological Society of London* 1892:500–505.
- Wagner CL, Eicher DJ, Katikaneni LD, Barbosa E, Holden KR (1999) The use of hypothermia: A role in the treatment of neonatal asphyxia? *Pediatr Neurol* 21(1):429–43.
- Wang SQ, Zhou ZQ (1999) Medical significance of cardiovascular function in hibernating mammals. *Clin Exp Pharmacol Physiol* 26(10):837–9.
- Zhou F, Zhu X, Castellani RJ, Stimmelmayer R, Perry G, Smith MA, Drew KL (2001) Hibernation: A model of neuroprotection. *Am J Pathol* 158(6): 2145–51.