



Telomere dynamics during hibernation in a tropical primate

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Abstract

Hibernation is a widespread metabolic strategy among mammals for surviving periods of food scarcity. During hibernation, animals naturally alternate between metabolically depressed torpor bouts and energetically expensive arousals without ill effects. As a result, hibernators are promising models for investigating mechanisms that buffer against cellular stress, including telomere protection and restoration. In non-hibernators, telomeres, the protective structural ends of chromosomes, shorten with age and metabolic stress. In temperate hibernators, however, telomere shortening and elongation can occur in response to changing environmental conditions and associated metabolic state. We investigate telomere dynamics in a tropical hibernating primate, the fat-tailed dwarf lemur (*Cheirogaleus medius*). In captivity, these lemurs can hibernate when maintained under cold temperatures (11–15 °C) with limited food provisioning. We study telomere dynamics in eight fat-tailed dwarf lemurs at the Duke Lemur Center, USA, from samples collected before, during, and after the hibernation season and assayed via qPCR. Contrary to our predictions, we found that telomeres were maintained or even lengthened during hibernation, but shortened immediately thereafter. During hibernation, telomere lengthening was negatively correlated with time in euthermia. Although preliminary in scope, our findings suggest that there may be a preemptive, compensatory mechanism to maintain telomere integrity in dwarf lemurs during hibernation. Nevertheless, telomere shortening immediately afterward may broadly result in similar outcomes across seasons. Future studies could profitably investigate the mechanisms that offset telomere shortening within and outside of the hibernation season and whether those mechanisms are modulated by energy surplus or crises.

Keywords Arousal · Captive · *Cheirogaleus* · Lemur · Torpor

Introduction

Hibernation is a widespread metabolic strategy employed by animals to survive seasonal environments (Geiser 2013). All major mammalian lineages have “heterothermic” members, i.e., species that can undergo torpor for a few hours to several days at a time (Carey et al. 2003; Mohr et al. 2020), including for example, Monotremata: short-beaked echidna (*Tachyglossus aculeatus*, Nicol et al. 2002), Marsupialia:

monito del monte (*Dromiciops gliroides*, Fontúrbel et al. 2022), Eutheria Eulipotyphla: hedgehogs (*Erinaceus roumanicus*, Rutovskaya et al. 2019), Eutheria Xenarthra: pichi (*Zaedyus pichii*, Superina and Boily 2007), Eutheria Chiroptera: little brown bat (*Myotis lucifugus*, Jonasson and Willis 2012), and Eutheria Rodentia: Arctic ground squirrel (*Spermophilus parryii*, Barnes and Ritter 1993). Even in tropical environments, faced with periods of food scarcity, heterothermic animals can reduce energetic demands by lowering their metabolism (Geiser and Mzilikazi 2011; Lovegrove and Génin 2008; Mzilikazi and Lovegrove 2005; Nowack et al. 2010).

Tropical hibernators, like their temperate counterparts, can experience multi-day torpor bouts interspersed with arousals, a return to “normal” or euthermic temperature conditions achieved through active thermogenesis (Dausmann 2014). Because hibernators alternate between torpid and euthermic states, they naturally experience drastic metabolic shifts without showing the harmful effects that would be

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experienced by non-heterotherms undergoing similar metabolic changes (Blanco et al. 2018; Carey et al. 2003; Landes et al. 2020). In other words, the physiological flexibility intrinsic to hibernation must include protective mechanisms to offset the metabolic stress presumably caused by torpor/arousal cycles (Hampton et al. 2010; Wu and Storey 2016). Intriguingly, and perhaps as a result of hibernation, hibernating species tend to live long lives for animals of their size (Blanco and Zehr 2015; Constant et al. 2020; Hoelzl et al. 2016a; Turbill et al. 2011; Wu and Storey 2016).

In recent decades, research on aging, metabolic stress, and longevity has converged on telomeres, the protective structural ends of chromosomes that have been traditionally considered markers of aging and cellular health (Chakravarti et al. 2021; Shay and Wright 2019; Trochet et al. 2015). In non-hibernators like humans and other primates, telomeres inexorably shorten over a lifespan of somatic cell division, ultimately leading to organismal senescence and age-related diseases (Burraco et al. 2022; Chakravarti et al. 2021; Shay and Wright 2019; Trochet et al. 2015). Telomere shortening or “erosion” can result from progressive mitotic activity, e.g., “replicative ageing” (Barnes et al. 2019) and cellular oxidative stress (Barnes et al. 2022; Brown et al. 2022; Koliada et al. 2015; Remot et al. 2022; Tobler et al. 2022; Wilbourn et al. 2018). If left unrepaired, telomere shortening can affect cellular integrity and ultimately cause cellular death (Brown et al. 2022; Engin and Engin 2021; Hemann et al. 2001; Monaghan and Ozanne 2018; Sun et al. 2015; Vettorelli and Passos 2017).

In hibernators, mitotic activity is severely reduced or halted during torpor bouts as a result of metabolic depression, but arousals may incur great cellular oxidative stress caused by metabolic spikes (Carey et al. 2003; Giroud et al. 2021) potentially affecting telomere integrity. Remarkably, hibernators seem to have the capacity to elongate telomeres to protect, prevent, and/or repair cellular damage. For example, telomere elongation via telomerase activity has been shown to occur in some hibernators like bats (Power et al. 2023). This is unlike non-hibernators, where telomerase activity is repressed in most somatic tissues as an anti-cancer evolutionary strategy (though telomerase activity in mammals may be more complex than previously thought, e.g., Pepke and Eisenberg 2022). Hence, telomere dynamics in hibernators may hold clues for understanding longevity and cellular senescence in mammals.

In temperate hibernators like the edible dormouse (*Glis glis*), the number of arousals and the time spent in euthermia, i.e., “normal” body temperature, had strong effects on telomeres: individuals that underwent more and longer arousals displayed greater telomere shortening (Hoelzl et al. 2016b). After hibernation, however, dormice with access to surplus food were able to

elongate telomeres. Thus, telomere elongation in dormice supports the notion that there are protective mechanisms in hibernators, while acknowledging inherent metabolic costs to telomere maintenance and regeneration (Hoelzl et al. 2016b; Ruf and Bieber 2020).

Telomere changes in a related species, the garden dormouse (*Eliomys quercinus*), showed similar patterns of shortening and elongation according to temperature conditions and food availability (Giroud et al. 2014). On the one hand, telomeres shortened when animals rapidly transitioned from low-temperature torpor to high-temperature euthermia, presumably as a result of oxidative stress during arousals (Nowack et al. 2019). In fact, those hibernating at warmer temperatures (14 °C) experienced less telomere attrition than those hibernating under colder conditions (3 °C) (Nowack et al. 2019). On the other hand, an individual's ability to repair telomeres was modulated by energy surplus. Garden dormice that were provisioned food during hibernation were able to elongate telomeres both under cold and warm temperature regimens (Giroud et al. 2023).

These studies on temperate hibernators suggest complex relationships between telomere dynamics, metabolic shifts, temperature conditions, and food availability. Are these relationships ubiquitous across hibernators, including animals inhabiting tropical environments? Dwarf lemurs (*Cheirogaleus* spp., suborder Strepsirrhini) are small-bodied, nocturnal primates endemic to Madagascar (Blanco et al. 2018; Fietz 2003). Although they are comparable in size to dormice, they naturally hibernate in the tropics (Blanco et al. 2018; Dausmann et al. 2005; Dausmann and Blanco 2016; Dausmann and Warnecke 2016). Whereas temperate hibernators can experience near-freezing conditions in nature, and undergo arousals from torpor at low temperatures, dwarf lemurs can hibernate under a range of temperature conditions, from 10° C to 30 °C, and can use temperature-stable or temperature-fluctuating hibernacula, e.g., inside tree holes (Blanco et al. 2018; Dausmann 2014). Dwarf lemurs are obligate hibernators in the wild, but can express only shallow metabolic depression under captive conditions when kept in warm rooms with daily food provisioning (Foerg and Hoffmann 1982). By restricting food and exposing individuals to cold temperature conditions during the winter, we successfully facilitated hibernation in fat-tailed dwarf lemurs (*C. medius*, median life span of 15 years; maximum life span of 29 years (Blanco and Zehr 2015) at the Duke Lemur Center (DLC), NC, USA (Blanco et al. 2021, 2022). When hibernating, DLC dwarf lemurs undergo multi-day torpor bouts of up to 11 days continually, interrupted by euthermic periods, i.e., arousals, lasting about 24 h (Blanco et al. 2021).

To investigate the relationship between torpor/arousal cycles and telomere dynamics, we transferred dwarf lemurs to temperature-controlled rooms to facilitate hibernation (11–15 °C) for approximately 4 months. If arousal-induced oxidative stress is a hallmark of hibernation, we predict that dwarf lemurs will show telomere shortening under cold conditions, when arousing from relatively low body temperature. Moreover, we predict telomere shortening to be related to the time spent euthermic (i.e., not torpid).

Methods

Study subjects and data analysis

We studied eight dwarf lemurs (4F, 4M; aged 1–16 years) from October 2020 to April 2021. At the DLC, dwarf lemurs were housed in small family units or solitarily in standard housing ($\geq 0.68\text{m}^3/\text{animal}$) under a North Carolina-like photoperiod (Blanco et al. 2021, 2022). During the active season (April–October), animals were maintained at 22–25 °C and offered food daily. During the hibernation season (between October 26 and March 4) individuals (mean $\pm$ SD pre-hibernation body mass = 286 ± 20 g) were housed in temperature-controlled rooms (11–15 °C) (Blanco et al. 2022). Under these conditions, dwarf lemurs underwent multi-day torpor bouts interspersed with arousals. These lemurs were offered food after accruing 24 h in euthermia, although they rarely ate. Water was freely available. To assess activity, individuals were outfitted with radio collars that detect skin temperature. An external data logger stored hourly readings per individual. We used the differential between skin and room temperature to determine torpor expression and time spent in euthermia based on published protocols (Blanco et al. 2022). Average days in torpor by dwarf lemurs progressively increased, e.g., from > 1 in November to > 4 in February. Maximum time spent continuously in torpor by a single animal was 8.9 days.

All dwarf lemurs were sampled in the pre-hibernation (mid-October), mid-hibernation (mid-January), end of hibernation (i.e., the day ambient temperatures were raised from 11–15 to 22–25 °C and daily food was provided),

post-hibernation (mid-March) and 1 month after the post-hibernation sampling (mid-April) (Fig. 1) periods. During the hibernation season, all individuals were either euthermic or arousing toward euthermia at the time of the sampling. During sampling, we collected epithelial cells from the lemurs' cheeks using PERFORMAgene oral swab kits (DNA Genotek Inc.). Oral swabs were stored in buffer at stable room temperature for up to 6 months until analysis.

DNA extraction and telomere length measurements

The samples were extracted according to the PERFORMAgene protocol. The relative telomere length measurement assay was adapted from the original methods by Cawthon (2002) and Park et al. (2013) and represents the ratio of two qPCR reactions: telomere over single copy gene (T/S). The single copy gene chosen for *C. medius* was POP7 (RNaseP), subunit p20.

For telomere (T), we used the following primers: Tel C [5'-TGTTAGGTATCCCTATCCCTATC-3'], at a final concentration of 200 nM, and Tel G [5'-ACACTAAGGTTTGGGTTTGGGTT-3'], at a final concentration of 400 nM. For the single copy gene (S), we used a mix of POP7f [5'-CCTTTTCTTCGCTTCCGTGG-3'] and POP7r [5'-TAC TTCCTCCGTTCCACCGT-3'], at a final concentration of 1 mM for both primers (for additional methodological details see Suppl. Mat.).

Both telomere and single copy gene PCR reactions were performed with QuantiFast SYBR Green PCR Kit (QIAGEN) on a LightCycler 480 real-time PCR machine. Twofold serial dilutions of genomic DNA, ranging from 10 ng to 0.3 ng/ μl (extracted from fat-tailed dwarf lemur blood) were used to create a standard curve, from which the concentrations of telomere reactions and single copy gene reactions were determined for each sample. The same reference DNA was used for all PCR runs. The T/S ratio for each sample was measured in triplicate wells, three times, in paired PCR runs (T-run followed by S-run, three times). When the duplicate T/S value and the initial value varied by more than 7% for any sample, it was run a third time and the two closest values were reported. All assays for the entire study were performed using the same lots of reagents.

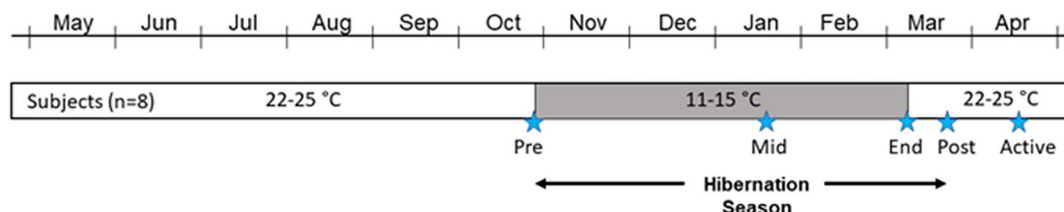
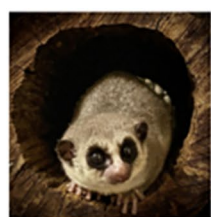


Fig. 1 Left: fat-tailed dwarf lemur at the Duke Lemur Center. Right: sample collection protocol: dwarf lemurs were sampled at pre-, mid-, end, post-hibernation and during the active season (light blue stars)

Data analysis and statistical tests

To determine the effects of time point on telomere lengths, we used a non-parametric, repeated-measures Friedman test implemented in GraphPad Prism (version 9.5.0). We included all five time points, i.e., pre-hibernation, mid-hibernation, end-hibernation, post-hibernation and active season. We used Dunn's post hoc tests to determine significant pairwise comparisons.

We also examined whether activity patterns were related to telomere dynamics. Specifically, we determined if hours in euthermia during the hibernation season correlated with telomere length by running a Spearman correlation between total hours in euthermia and daily change in telomere length (DTL) during hibernation. We computed DTL to account for the disparity in total telomere length across individuals and the different number of days between sampling events. DTL was calculated by subtracting the difference in telomere length from pre-hibernation to end-hibernation divided by the number of days between sampling.

Results

We found an overall significant effect of time point (Friedman statistic = 13.7, $p = 0.008$), with telomeres maintaining length or elongating during hibernation, but shortening directly afterward (Fig. 2). Post hoc tests clarified that telomeres were longer on the last day of hibernation compared to both the post-hibernation ($p = 0.044$) and active season ($p = 0.027$) sampling time points (Fig. 2a). We thus detected telomere shortening following the hibernation season, despite there being only a 2-week period between the sampling points at end-hibernation and post-hibernation. Nevertheless, we did detect great variation between individuals (Fig. 2b). Several females showed the biggest changes in telomere lengths through time, albeit our sample sizes limited statistical resolution.

During the hibernation season, the degree of telomere lengthening related to the time spent euthermic: dwarf lemurs that spent more time in euthermia during the

hibernation season showed relatively less telomere lengthening than did dwarf lemurs spending less time in euthermia (Spearman correlation test: $r = -0.8095$, $p = 0.0218$; Fig. 3).

Discussion

We observed variable telomere lengthening in dwarf lemurs as the hibernation season progressed, with the degree of lengthening negatively correlating to time spent in euthermia, followed by significant telomere shortening in the weeks after the end of hibernation. If telomere maintenance or elongation is a mechanism to offset cellular stress in hibernators, one major question raised by our results is why dwarf lemurs would shorten telomeres directly after hibernation? These patterns are unlike what is commonly reported for temperate hibernators, wherein telomeres shorten *during* hibernation under food deprivation, but lengthen afterward under food provisioning (Hoelzl et al. 2016b). Our results also differed from those of Nowack et al. (2019) who found dormice hibernating at, and arousing from, colder versus warmer temperatures experienced greater telomere shortening. Perhaps, our results point to biological differences

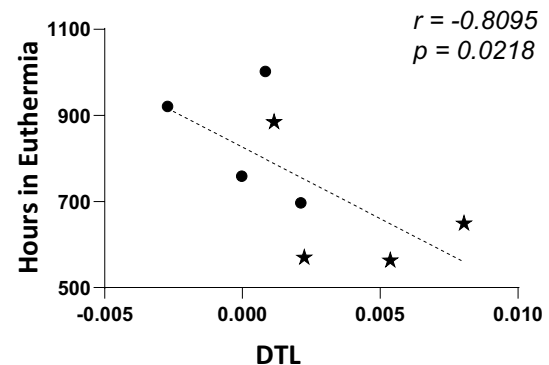


Fig. 3 Daily change in telomere length (DTL) during hibernation against time spent in euthermia. R and p values determined via Spearman correlation. Females are represented by stars, and males by circles.

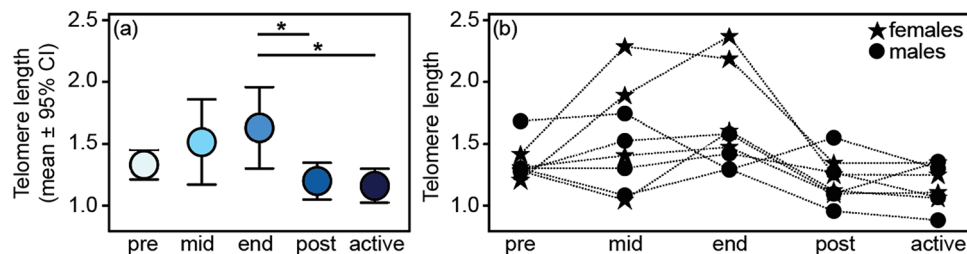


Fig. 2 Telomere length at five sampling time points, including **a** average lengths across individuals with error bars indicating 95% confidence intervals (CI) and **b** individual values for all female (stars) and male (circles) study lemurs. Statistics can be found in the text; * $p < 0.05$

between temperate rodent models and tropical primates (Steinert et al. 2002; Trochet et al. 2015).

One potential explanation is that telomere maintenance/elongation in dwarf lemurs during hibernation is an essential counterstrategy to cope with the oxidative stress incurred during arousals. This strategy may be favored preemptively if individuals would otherwise approach critical short telomere length that could impair cellular functionality, i.e., the “last resort elongation hypothesis” (Haussman and Mauck 2008; Tobler et al. 2022). Indeed, preemptive elongation has been suggested to occur in dormice with access to surplus food before hibernation (Hoelzl et al. 2016b). Alternatively, perhaps the discrepancies between systems are simply due to differences in experimental design, and additional studies of other tropical hibernators and heterothermic primates are warranted to confirm the findings.

At the onset of the active season, we found consistent and significant telomere shortening. Telomere length then remained virtually unchanged during the month following the post-hibernation time point. Emergence from hibernation in dwarf lemurs is linked to the initiation of the reproductive season, which is energetically challenging for males that must develop testes in anticipation of mating (Fietz and Dausmann 2003). Hence, telomere shortening directly following hibernation may be associated with cellular and physiological stress from hormonal reconfigurations, increased locomotor activity, and restitution of physiological functions (e.g., sleep and growth) (Speakman 2008) that may have been restricted to interbout arousals or completely arrested during hibernation. Overall, perhaps this telomere shortening acts as a “reset” to pre-hibernation lengths with little implication for animal aging or health, because in the end, telomere length did not significantly differ between pre- and post-hibernation periods.

Our result that the degree of telomere lengthening during hibernation is inversely correlated to time in euthermia supports the notion that torpor per se may not affect telomere integrity, but arousals and/or time in euthermia can affect both telomere length by means of shortening due to increased oxidative stress, or by means of lengthening through repair mechanisms to counteract oxidative stress. Evidence of telomere shortening or “degradation” under environmentally harsh conditions and subsequent telomere elongation has also been documented in non-hibernating mammals and birds (Brown et al. 2022; Criscuolo et al. 2020) and it is consistent with the “metabolic telomere attrition” hypothesis that posits telomere attrition is greatest when individuals undergo harsh energetic constraints (Casagrande and Hau 2019; Power et al. 2023).

Captive dwarf lemurs may be uniquely suited as models in which to investigate telomere dynamics because they can express great physiological breadth under different environmental conditions. It is important to note, however,

that our small sample size coupled with limited sampling renders the results reported here preliminary. The scarcity and protected status of these lemurs (we are unaware of any breeding colonies other than at the Duke Lemur Center) limits opportunities for replication and more rigorous and invasive sampling protocols. However, future studies could profitably investigate the putative protective mechanisms that offset telomere shortening within and outside of the hibernation season, and whether those mechanisms are reliant on energy surplus or crises.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00360-024-01541-9>.

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Author contributions MBB: conceptualization, funding acquisition; formal analysis, sample collection, writing—original draft; DLS, LJ: methodology, formal analysis, review and editing; LKG: formal analysis, visualization, writing—original draft; ADY, EEE: supervision, review and editing; PHK: conceptualization, review and editing. All authors gave final approval for publication.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors have no competing interests to declare that are relevant to the content of this article.

Ethics statement Research protocols used in this study were approved by the Duke Lemur Center Research Committee and by Duke University Institutional Animal Care and Use Committee, under protocols A263-17-12 and A213-20-11. These protocols followed guidelines established by the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health.

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