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Cold is hot for slowing aging

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Torpor

Cold is hot for slowing aging

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Abstract

Hrvatin and colleagues explore the anti-aging mechanisms of torpor, separating the roles of metabolic rate and body temperature. The study demonstrates that hypothermia, not hypometabolism, drives epigenetic aging deceleration positioning body temperature as a pivotal target in aging research.

Main

Species capable of entering torpor—commonly referred to as hibernators—tend to have longer lifespans than mammals of comparable body size. Metabolism and body temperature are strongly related to aging. However, their respective roles in aging of hibernators remained unclear. Mammals, which maintain a core temperature near 37 °C, compensate for heat loss by adjusting their metabolic rate according to body mass and surface-to-volume ratio. Smaller mammals lose heat more rapidly and thus must generate more heat per unit of body mass than larger animals. However, some mammals are capable to actively reduce metabolic rate through torpor or hibernation ¹. Torpor itself can last from a few hours to several weeks, characterized by a dramatic decline in metabolic rate accompanied by a temperature decrease generally proportional to the thermal gradient with the environment. Heart rate, respiration, locomotor activity, and other vital physiological parameters follow this downward trend, effectively standby most cellular processes. A succession of extended torpor bouts, separated by brief 24-hour arousal phases, constitutes hibernation. The prevailing explanation for the longevity of hibernators has generally been the cumulative effect of extended periods at a low metabolic state ²; however, recent evidence suggests a possible role for temperature ³. Now Jayne and co-workers demonstrate that low body temperature—rather than low metabolic rate—is central to torpor’s anti-aging effect ⁴.

Figure title: Hypothermia and aging

INSERT FIGURE

Legend: Figure 1 illustrates that the torpor-induced slowing of aging is driven by hypothermia, rather than hypometabolism or caloric restriction.

Until recently, natural torpor was the only available model for study. Mice, however, are facultative heterotherms that can enter torpor as a defense against negative energy balance ⁵. Over the past decade, researchers have begun to unravel the neural pathways underlying torpor induction, thanks to the powerful genetic toolbox available for these rodents. ⁶⁻¹⁰. These findings enabled laboratories to induce Torpor-like States (TLS) in mice via opto- or chemo-genetic ⁷⁻¹⁰, or even physical means ¹¹. Among these methods, chemogenetic activation of neurons within a small anteroventral region of the medial and lateral preoptic area (avMLPA) of the hypothalamus was shown by a previous work from the same research group to replicates many hallmarks of torpor in mice ⁷.

Typically, TLS-inducing methods generate torpor bouts lasting a few hours. Jayne and colleagues, however, devised a protocol extending a single torpor episode to several days and introduced a means of delivering the chemogenetic neuronal activator clozapine N-oxide (CNO) in drinking water. By cycling between CNO-treated water and drug-free water, they induced a nine-month torpor–wakefulness rhythm, closely approximating natural hibernation. Building on this innovative framework, which permits control over both the duration and depth of torpor, the authors addressed a pivotal question in aging research: Does the slower aging seen in torpor stem primarily from a reduction in metabolic rate, or from a drop in body temperature?

In nature, hypothermia and hypometabolism are inextricably linked. Yet, by applying their new protocol, the team managed to disentangle these factors. To accomplish this, they induced torpor for three months in mice housed at thermoneutrality (32 °C). Although these mice displayed metabolic rates comparable to

torpid mice housed at 22 °C, their body temperature remained significantly higher due to the warmer ambient conditions. Notably, only the group experiencing low body temperature showed a slowdown in epigenetic aging, suggesting that it is hypothermia—rather than hypometabolism—driving this phenomenon. To further probe the mechanism, the authors investigated whether the well-known lifespan benefits of caloric restriction (CR) could account for torpor's anti-aging effect. Because CR protocols regularly induce torpor in mice, they tested caloric restriction alone and caloric restriction plus TLS at thermoneutrality against TLS with hypothermia. Surprisingly, neither condition reproduced the aging slowdown observed in the low-temperature group.

A notable aspect of this study lies in how aging was assessed. The blood epigenetic clock has gained popularity as an effective metric of aging, yet both aging and torpor affect diverse cells and organs in varied ways. Intriguingly, the authors detected a clear slowdown in blood epigenetic aging, but the effect was weaker in the liver and negligible in other tissues. These findings highlight the need for broader, multi-organ comparisons in future investigations.

It is widely acknowledged that the brain initiates metabolic suppression—whether in animals exhibiting daily torpor triggered by ambient cues or in those undergoing circannual hibernation cycles. Neural tracing experiments in mice are unraveling the torpor circuit, currently centered along the main thermoregulatory axis: the Preoptic Area–Dorsomedial Hypothalamus–Raphe Pallidus. Even if these insights are accurate, the question remains: how does a neural command orchestrate a torpor response at the cellular level throughout the body? In chronobiology, a parallel conundrum exists: how does the suprachiasmatic nucleus synchronize peripheral clock genes in every cell? The prevailing solution invokes a systemic signal such as the circadian temperature oscillations¹². By analogy, one might speculate that the brain reduces signals to specific heat-generating, metabolically active tissues while blocking compensatory responses, with temperature shifts and changes in blood parameters (including pCO₂ and other factors yet to be uncovered) acting as global cues for cells to engage a torpor protocol, i.e. to activate the yet-to-be-identified set of genes required to adapt to the new low metabolism condition. The present findings appear to support this view, revealing that metabolically active organs like the liver experience a greater impact on aging deceleration than do other organs, while the most anti-aging effects are observed in blood.

An additional question is whether hypothermia induced by TLS confers the same anti-aging advantages as externally imposed cooling. No standardized method currently exists to match the duration and depth of cooling outlined in this study, but such protocols hold strong translational promise. Torpor is known to bolster resilience against injuries such as hypoxia, ischemia–reperfusion, and radiation. Would mere hypothermia replicate these protective properties, or does torpor entail something beyond a drop in temperature? This is a very relevant question for all the prospect to use some sort of torpor-like state as a countermeasure to the many detrimental effects of space travel¹³. Notably, torpor-induced hypothermia is undefended, i.e. lacking sympathetic activation to counteract falling temperature. Could reduced body temperature in the absence of catecholamine release be central to torpor's anti-aging effects? In translational terms, it is worth noting that many methods successfully used to induce TLS in mice do not produce similarly powerful effects in non-hibernators such as rats. In this species, only two approaches have been shown to induce deep, undefended hypothermia: inhibiting neurons within the Raphe Pallidus¹⁴, and activating central adenosine A1 receptors¹⁵. Looking ahead, these strategies may offer a means to harness the anti-aging potential of hypothermia.

Another intriguing outcome of this research is the apparent lack of sex-specific differences. Females typically enter torpor more readily and sustain longer bouts, suggesting a deeper or more efficient torpor state. Testosterone—a hormone that inhibits torpor—is generally diminished in seasonal hibernators prior to hibernation, yet their hibernation duration remains shorter in males. In this study, no such sexual dimorphism emerged, implying that central pathways driving torpor may supersede hormonal influences.

In conclusion, this work opens a fresh view in aging research by placing body temperature center stage once again. As we learn more about the interplay between thermal regulation and metabolic pathways, the possibility of harnessing torpor-like states to slow aging becomes an enticing prospect. Live cold—and prosper.

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Competing interest statement

I have no competing interest to declare.