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REVIEW

Hot take on a cool topic: is there really a need for a systemic master mediator of metabolic suppression in mouse daily torpor?

[version 1; peer review: 2 approved, 1 approved with reservations]

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v1 **First published:** 28 Aug 2026, **11**:561
https://doi.org/10.12688/wellcomeopenres.27516.1
Latest published: 28 Aug 2026, **11**:561
https://doi.org/10.12688/wellcomeopenres.27516.1

Abstract

We argue in this perspective that daily torpor in the mouse, induced by a lack of caloric intake and a relatively cool environment, does not require a dedicated “master mediator” for systemic metabolic rate (MR) suppression. Instead, a set of centrally mediated changes, most notably: cessation of physical activity; dramatically reduced thermogenesis, along with a lowering of the defended minimum body temperature (Tb); and, reduced cardiovascular work, together drive the substantial drop in metabolic rate at the initiation of daily torpor in the mouse. That is, rather than invoking a global, organism-wide suppression of metabolism across all tissues, we argue that MR reduction during mouse daily torpor is selective and physiologically organized, targeting a small number of energetically dominant organ systems. Once Tb has declined in response to the initial physiological adaptations, temperature-dependent effects on biochemical reaction rates can account for much of the further reduction in whole-animal MR during the torpid state, resulting in an ultimate fall in MR of 75–80% in daily torpor of the mouse. This framework also aligns torpor with the normal ultradian rhythm of sleep-associated reductions in MR and Tb, differing mainly in the much deeper nadir reached.

Plain Language summary

The question: When a mouse goes into daily torpor (a short-term, deep energy-saving state triggered by fasting or cold), does the body need some kind of master “off switch” that shuts down metabolism everywhere at once — the way many researchers have assumed for hibernators?

Open Peer Review

Approval Status ✓ ✓ ?

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version 1 28 Aug 2026	✓ view	✓ view	? view

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Any reports and responses or comments on the article can be found at the end of the article.

The authors' answer: no, not for mice. They argue you don't need to invoke any special whole-body metabolic suppressor. Instead, the big drop in metabolic rate during mouse daily torpor can be fully explained by a handful of ordinary, centrally controlled changes plus simple physics:

1.
Getting less active — the mouse stops moving and stops digesting food. This saves some energy, but most of that saving already happened when it fell asleep, before torpor even started.

Add these up and you get the observed 75–80% drop in energy use during torpor — without needing to propose a special systemic mechanism that actively "turns off" cells everywhere.

Keywords
torpor, hibernation, metabolism, body temperature

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Author roles: Ambler M: Conceptualization, Funding Acquisition, Resources, Writing – Original Draft Preparation, Writing – Review & Editing; **Pickering A**: Conceptualization, Funding Acquisition, Supervision, Writing – Review & Editing; **Swoap S**: Conceptualization, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: This work was supported by the Wellcome Trust [308526] and the Biotechnology and Biological Sciences Research Council [BB/W007266/1].
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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How to cite this article: Ambler M, Pickering A and Swoap S. **Hot take on a cool topic: is there really a need for a systemic master mediator of metabolic suppression in mouse daily torpor? [version 1; peer review: 2 approved, 1 approved with reservations]** Wellcome Open Research 2026, **11**:561 https://doi.org/10.12688/wellcomeopenres.27516.1

First published: 28 Aug 2026, **11**:561 https://doi.org/10.12688/wellcomeopenres.27516.1

When we consider the scale of endotherms, to state the obvious, the mouse is small. Similar creatures to the mouse, like the shrew and hummingbird live on the edge of existence. Their small size results in a massive surface area-to-volume (SA/vol) ratio. For example, with a surface area of 75 cm^2 (Dawson, 1967) and a body weight of 25 g, the SA/vol ratio of the mouse is some 14x higher than that of a human. Because heat loss occurs across the surface area while heat is generated by body volume (a surrogate for tissue mass), up to 30% of total energy expenditure is directed to thermogenesis in the mouse at 22 °C ambient temperature (Reitman, 2018). Hence, small endotherms face a precarious balance when food is scarce. Their lives are centered on acquiring and storing energy, through foraging, eating, caching and fat-accumulation, to fuel the heat-generating engines. Since such animals only have limited space for fat reserves, even a short fast can be disastrous. As a result, in the absence of food, many small mammals suspend 'normal' homeostasis to reduce their metabolic demands. This reduced metabolism results in the state of daily torpor, where most physiological activities are reduced. Indeed, if a fasted mouse were to maintain the high MR required for normal homeothermy, it would rapidly exhaust its limited energy reserves. In this context, torpor is a protective strategy that prevents catastrophic energy depletion.

In contrast, when exposed to cool ambient temperatures in the presence of food, mice increase intake and elevate their metabolic rate, to maintain body temperature (Hudson & Scott, 1979). Hence, bouts of daily torpor can be prevented by hormonal signaling that indicates the presence of fuel, either as stored fat, a recent meal, or the expectation of a meal, allowing the heat producing engines the fuel needed to defend a 'normal' minimum T_b (Gavrilova et al., 1999; Van Der Vinne et al., 2018). Further, fasted mice given the choice between a cool or warm environment preferentially choose the warm one, thereby avoiding torpor (Craig et al., 2021). As such daily torpor in the mouse is a physiological response of last resort.

The metabolic benefits of torpor can be enormous, even lifesaving (Geiser & Brigham, 2012; Koizumi et al., 1996; Lyman et al., 1981). The metabolic rate during torpor is well below even the basal metabolic rate (the MR from cellular activities in the absence of physical activity and thermoregulatory heat production), resulting in substantial energy savings up to 75–80% in the mouse (Geiser, 2004; Hudson & Scott, 1979; Nestler, 1990b; Ruf & Geiser, 2015). This raises the important question of how these small mammals achieve the energy savings of daily torpor: is there a global signal that triggers widespread suppression of cellular metabolism in response to food deprivation in the mouse?

Torpor has long been assumed to require an "active system-wide metabolic suppression" (Geiser, 1988a, 2004; Heldmaier et al., 2004). Indeed, there is a great deal of evidence from many mammals entering torpor that MR falls before T_b, including mice (Nestler, 1990a, 1990b; Udoh et al., 2024), suggesting an active metabolic suppression. This is not a point of dispute. Rather, we argue here that the daily torpor seen in a mouse does not require a solution that invokes *systemic* suppression of metabolism. We argue that metabolic suppression during mouse daily torpor is selective and physiologically discretely coordinated, targeting only a small number of energetically dominant organs. Indeed, only a few targeted core physiological changes, initiated centrally (i.e. by the brain) that modulate organ-level metabolism are sufficient to suppress metabolism to the level needed to initiate torpor in the mouse. Those key allostatic changes to move from an active state, initially to a sleep state and thence to a torpid state are 1) cessation of physical activity, 2) decreased thermogenesis in a cool environment via altered autonomic outflow, 3) decreased cardiorespiratory work mediated via the autonomic nervous system and the respiratory control network, and 4) cessation of metabolic activity associated with food intake and digestion. Once those changes have been made and the animal no longer defends a euthermic T_b, significant and rapid reductions in oxygen consumption would be achieved. Subsequently, the continued decline in MR and T_b follow passively from the temperature-dependence of underlying biochemical reactions. Collectively these alterations of regulatory set points and behavioural changes are likely to be sufficient to achieve the target of energy conservation without the need to invoke a separate process that switches off metabolism at the cellular level (such as via mitochondrial inhibition).

Ultradian rhythms are those behavioural/physiological changes that occur more frequently than once per day and are seen in species throughout the animal kingdom (Blessing & Ootsuka, 2016; Meyer et al., 2012; Škop et al., 2024). Mice display such ultradian rhythms in metabolic rate, T_b, heart rate, activity, and blood pressure every 2–3 hours corresponding directly with the wake/sleep cycle (Škop et al., 2024). When the mouse is awake, it 1) is physically active, 2) has brown adipose tissue (BAT) activation via the sympathetic nervous system, and 3) has an autonomically-mediated increased heart rate and blood pressure, resulting in an elevated metabolic rate and a higher defended minimum T_b. Metabolic rate and T_b drop substantially at the end of these active periods. When the mouse sleeps, it achieves a lower metabolic rate through cessation of physical activity; reduced cardiac work; lower BAT activity; and a lower defended T_b. Because of its small size and the resultant thermal lability (Gordon, 2012), simply decreasing physical activity, slowing heart rate, and decreasing BAT activity results in a 1.5–2 °C T_b drop

between the active state and sleep state (Škop et al., 2024). It appears that the mouse defends this new lower T_b - presumably through continued partial activation of heat generation pathways.

Torpor bouts reliably occur at the end of an ultradian "active state" (and often a "hyper-active" state), and typically near the end of the dark phase (Van Der Vinne et al., 2018). Mice enter torpor through a sleep state (Huang et al., 2021; Lo Martire et al., 2020), and so some metabolic savings occur when the mouse falls asleep but before torpor starts. We hypothesise that further changes in those same parameters (physical activity, degree of cold-induced thermogenesis, cardiac work) plus the additional impact of lower T_b on enzymatic activity is all that is needed to explain the fall in metabolic rate seen in mouse daily torpor. Let's parse the role of each one of those parameters in the contribution to a torpid metabolic rate, starting with physical activity.

Reduced physical activity: moderate metabolic gains when moving from sleep to torpor

When mice fall asleep, they obviously become inactive, so there are limited metabolic savings from reduced physical activity in the torpid mouse beyond the gain from falling asleep. However, the additional reduction in respiratory rate from ~100–150 breaths/minute when asleep to ~10–20 breaths/minute in torpor would allow some further metabolic savings (Morhardt, 1970). Similarly, while a sleeping fed mouse continues to expend energy on digestion, a fasted torpid mouse has minimal food in its gastrointestinal tract, so there would be some metabolic savings from this in torpor.

Reduced thermogenic activity: greater than 25% saving of active metabolic rate

Non-shivering thermogenesis, unlike physical activity, is greatly reduced when moving from sleep to torpor. The sleeping mouse has some thermogenic activity (dependent upon the ambient temperature), likely from heat generation from brown fat and/or skeletal muscle that defends their T_b while asleep (Szentirmai & Kapás, 2014). Therefore, there is room to reduce metabolic expenditure should the mouse no longer defend a T_b of ~35 °C. Non-shivering thermogenesis alone can contribute up to 60% of the total metabolic rate in the cold-adapted and euthermic mouse (Cannon & Nedergaard, 2011). The mouse saves about 25% of total energy expenditure when decreasing BAT activity as it moves from the active state to sleep state (Škop et al., 2024). Based on these data, the savings the mouse gained by moving from sleep to torpor would be between 25 to 60% of an active mouse's metabolic rate.

Reduced cardiac work: at least 10% saving of active metabolic rate

Torpor reduces cardiac work by reducing heart rate and cardiac output. During sleep the mouse heart rate reduces from ~650 to ~475 beats per minute and mean arterial pressure from ~125 to ~105 mmHg, which has been estimated to result in a 6% reduction in metabolic rate (Škop et al., 2024). During entrance into daily torpor in the mouse, and before any significant change in T_b, heart rate and mean arterial pressure reduce further compared to sleep, with a fall to ~275 bpm and ~ 80 mmHg, respectively (Swoap & Gutilla, 2009). Indeed, it has been long known that the parasympathetic drive to the heart is strongly engaged at entrance into torpor (Harris & Milsom, 1995; Morhardt, 1970; Williams et al., 2002). Further, the direct cooling effect on the cardiac pacemaker function will serve to only increase energetic savings, as heart rate and mean arterial pressure continue to fall to a minimum of 70 bpm and 60 mmHg at the temperature nadir of the torpor bout in the mouse (Swoap & Gutilla, 2009). The slowing of heart rate and lowering of blood pressure reduces cardiac work, which we estimate to be an additional 10% of the active metabolic rate at the onset of torpor.

Reduced enzyme activity (Q_{10} effect): 8% of active metabolic rate per °C

We propose here that the effect of a reduced T_b on the rate of enzymatic reactions within cells makes up the lion's share of the savings. We are by no means the first to make this suggestion (Geiser, 1988a; Heldmaier & Ruf, 1992; Staples et al., 2022). This was a hotly debated topic in the hibernation community a few decades ago. Active systemic suppression of metabolism beyond physiological adaptations and reduced body temperature was proposed, at least in seasonal hibernators, for a few reasons: 1) thirteen-lined ground squirrels and the edible dormouse, both deep hibernators, appear to suppress metabolism below basal metabolic rate without a fall in T_b when housed in thermoneutrality (Heldmaier & Elvert, 2004; MacCannell & Staples, 2021; Staples et al., 2022), 2) Q_{10}, the ratio of the rate of activity (of an enzyme or biological system) at two different temperatures that are 10 °C apart, is typically between 2–3. However, the measured Q_{10} of the MR for some hibernators is well above 3 (see (Lawrence Chia-Huang Wang & Hudson, 1971) for an example), suggesting an active suppression of metabolism in addition to the passive effect of cooling on metabolism. Q_{10} may not be, in general, an adequate framework for analyzing MR-T_b relationships in heterothermic endotherms when thermal conductance can vary (see also below). Hence, changes in MR cannot be unambiguously attributed to intrinsic temperature effects on biochemical processes, as thermoregulatory responses and altered heat loss can obscure or dominate the relationship between T_b, ambient temperature, and MR (Heldmaier & Ruf, 1992). Notwithstanding that caveat, cellular metabolism and biochemical reactions are not impervious to the impact of temperature on their activity. One estimate for the Q_{10} of the overall metabolic rate in heterotherms is around 2.2–2.3 (Geiser, 1988b). Given this conservative estimate for Q_{10}, the cellular metabolic rate - not modified by anything but temperature - will drop about 8%

per 1 °C just due to physical properties of the enzymes themselves. When fasted at an ambient temperature of 22 °C, mice reliably reach a core temperature of 25 °C or lower. From a starting T_b of 36 °C, this equates to a 60% metabolic saving from Q_{10} effects alone: enough to explain the 75–80% metabolic savings of *daily* torpor in the mouse (Hudson & Scott, 1979; Nestler, 1990b). That is, the observed reductions in T_b during torpor are sufficient to explain the majority of the decline in MR *following* torpor entry, without invoking an additional, global coordinated suppression of metabolism. This conclusion does not exclude the possibility of active metabolic depression, nor does it deny its existence in other contexts such as hibernation; rather, it supports the hypothesis that temperature-dependent effects alone are quantitatively adequate to account for the post-entry decrease in MR in daily torpor in the mouse.

Daily torpor: a summation of behavioural, physiological and biochemical savings

The fact that metabolic rate falls before T_b is one of the defining features of torpor, and our model fully captures this sequence. Crucially, this drop in MR does not reflect a systemic master mediator. Rather, we believe the "active metabolic suppression" is a consequence of continued physical inactivity and cessation of food intake associated with the sleep state, the decrease in non-shivering thermogenesis via reduced sympathetic outflow, and decreased cardiac work via elevated vagal outflow. As these energy consuming and heat-producing activities are suppressed, oxygen consumption immediately falls, followed by T_b as heat is lost to the environment. Without active defense of a euthermic T_b, there is a subsequent and substantial additional reduction in metabolic rate as enzymatic activity slows in a temperature-dependent manner (see Figure 1). These changes reflect central involvement of just a few important organ systems and subsequent intrinsic slowing of cellular processes – all cells will demonstrate reduced oxygen consumption (not just muscle and BAT) via the influence of temperature on the efficiency of enzymatic catalysis of reactions in cells. The combination of the metabolic savings from these components is at least 50% of the active metabolic rate. Even in the face of heat conductance to the environment that does not change or decreases slightly with torpor (Geiser, 2004; Sunagawa & Takahashi, 2016), T_b will consequently plummet. This model of daily torpor in the mouse states that the "active metabolic suppression" seen at the onset of torpor may only be a centrally-mediated inhibition of just a few select organs. Unlike hibernators, daily torpor in the mouse does not require a special mechanism or a global metabolic inhibitor. Rather, torpor in the mouse only requires a centrally generated decrease in adaptive thermogenesis in a relatively cool environment, and cessation of defense of a minimum T_b of 35 °C. Metabolic rate drops before T_b, but the drop in T_b is critical for the nadir low metabolic state.

Metabolic rate in 'synthetic torpor'

Over the past few years, several experimental models that chemogenetically or optogenetically drive torpor have emerged (Hrvatin et al., 2020; Takahashi et al., 2020; Zhang et al., 2020). This has been termed 'synthetic torpor' to highlight the fact that it is induced solely through central neuronal activation in the absence of a 'natural' trigger for torpor (i.e. fasting). Synthetic torpor provides a key paradigm for exploring the mechanisms underlying the metabolic savings associated with torpor. Whereas fasting in a *thermoneutral environment* largely prevents natural torpor (Craig et al., 2021), it is still possible to induce synthetic torpor in a warm environment. Inducing synthetic torpor in an ambient temperature of 20 °C results in an approximately 75% reduction in oxygen consumption. In contrast, inducing synthetic torpor at a thermoneutral temperature of 32 °C results in minimal changes in T_b and oxygen consumption (Takahashi et al., 2020). These observations support the argument that most of the energy savings associated with torpor in the mouse are due to physiological adjustments of thermogenesis and Q_{10} effects, rather than a system-wide signal that directly puts the brakes on cellular metabolism. Of course, it is possible that models of synthetic torpor recapitulate only certain elements of natural torpor, but to date we are unaware of any evidence from a model of synthetic torpor that demonstrates suppression of oxygen consumption in the absence of a reduction in T_b.

We should however "bear" in mind that the mechanisms of torpor may vary across species with very different dimensions and different torpor patterns (i.e. daily versus seasonal). Unlike mice, bears are massive, with a correspondingly much-smaller SA/vol ratio. It is perhaps unsurprising then, that hibernating black bears reach a nadir T_b of around 30 °C and average around 33 °C. This poses a challenge if hibernating bears were to rely heavily on Q_{10} effects to reduce metabolic demand. Assuming a Q_{10} of 2.2, this would produce only a 27% reduction in oxygen consumption as the bear's body temperature drops from 37 to 33 °C. Despite these modest reductions in T_b, black bears achieve an approximately 75% reduction in oxygen consumption during hibernation (Tøien et al., 2011). Furthermore, during emergence from hibernation the resting oxygen consumption remains approximately 50% of summer levels even as T_b reaches normal levels. Together, these observations do argue in favour of an active suppression of metabolism in larger seasonal hibernators, in contrast to the model of daily torpor in the mouse.

So where does this leave the study of torpor as a model for medical translation? Unless future work on bears can identify a 'master metabolic regulator', due to the larger size and relatively low SA/vol of human (akin to the bear), to achieve significant metabolic suppression would likely require active cooling alongside induction of synthetic torpor. However,

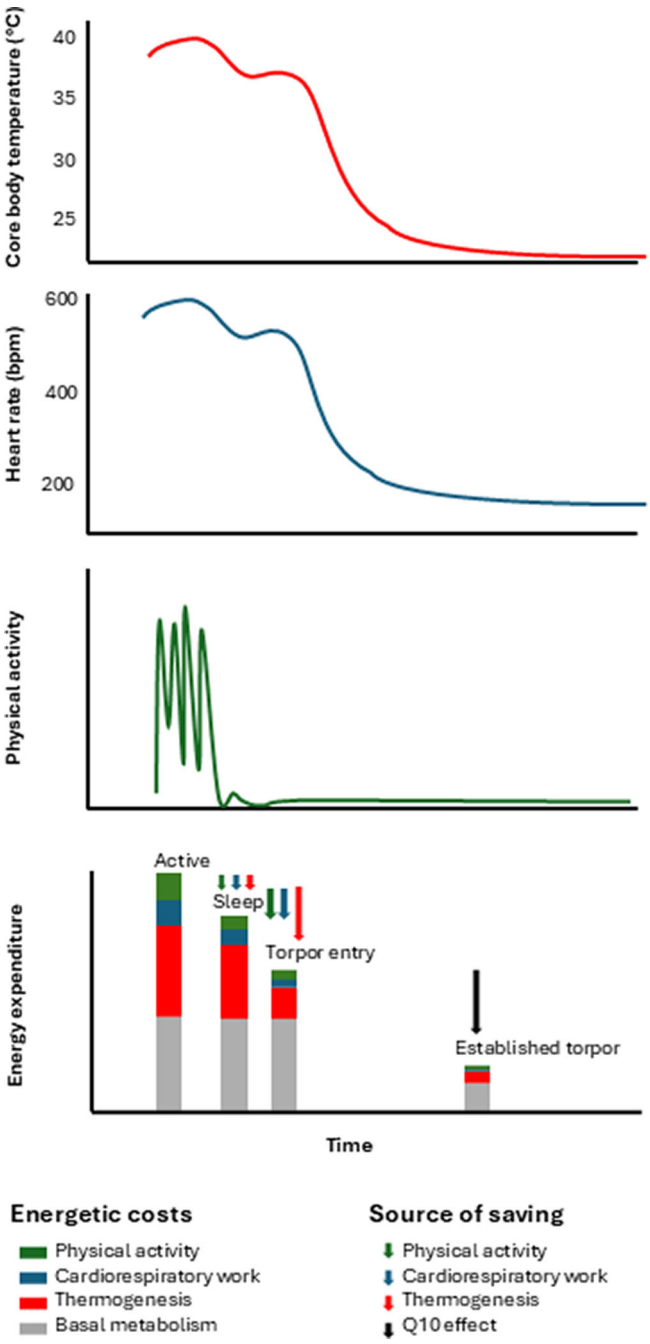


Figure 1. Schematic representation of torpor in relation to active and sleep states. Arrows represent source of metabolic savings associated with transition between each state. Early torpor differs from sleep primarily through reductions in thermogenesis, which provides the initial savings in torpor. Subsequently, Q10 effects dominate as temperature drops in established torpor. **Note**, this is a hypothetical proposal and is not intended to be interpreted as supportive data.

there would still be merit in this approach: Q_{10} effects would generate significant metabolic savings. In this case, the aim of inducing synthetic torpor would be to modulate the central nervous system control circuits such that the normal counter-regulatory defence responses to physical cooling are not engaged. Indeed, it is likely that these counter-regulatory responses limit the usefulness of therapeutic hypothermia in previous clinical trials (Dankiewicz et al., 2021; Dundee et al., 1953; Le May et al., 2021; Sandestig et al., 2014).

Data availability statement

No data are associated with this article.

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Current Peer Review Status: ✔ ✔ ?

Version 1

Reviewer Report 30 September 2026

https://doi.org/10.21956/wellcomeopenres.30285.r166532

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Overall Impression:

The authors present a conceptually clear and thought-provoking perspective on the energetics of daily torpor in mice. I found the quantitative framework useful. The combined effects of reduced locomotor activity, suppression of brown adipose tissue (BAT) thermogenesis, decreased cardiac workload, and temperature-dependent Q10 effects could together account for the 75–80% reduction in VO2 observed during fasting-induced torpor (FIT) in mice. As an organ-level energy budget, I think this is a reasonable and useful way to look at the problem.

My main concern is the broader conclusion drawn from this calculation. The fact that the numbers can largely account for the reduction in whole-body VO2 does not by itself show that a “master mediator” or upstream coordinating mechanism is unnecessary. These are two different questions: one is where the reduction in energy expenditure comes from, and the other is what signal initiates and coordinates these changes across the body. The current manuscript should more clearly distinguish these levels of explanation.

I have several specific comments.

1. Target-Tissue Specificity Does Not Distinguish Humoral from Neural Regulation

The authors argue that the reduction in VO2 can largely be explained by suppression of a limited number of energetically important tissues, including BAT, skeletal muscle, and the heart, together with passive Q10 effects. Based on this, they suggest that there is little need to consider a systemic master mediator. My concern is that this conclusion goes beyond what the calculation supports.

I am not fully convinced by this argument. It seems to assume that a circulating humoral mediator would act broadly and indiscriminately across peripheral tissues. However, that need not be the case. In classical endocrinology, circulating signals can produce highly tissue-specific effects because receptor expression, receptor density, downstream signaling pathways, and tissue

accessibility differ between organs.

Therefore, selective suppression of BAT, skeletal muscle, and cardiac metabolism would still be compatible with a circulating mediator, if its relevant receptors are selectively expressed in these tissues or in specific upstream central circuits controlling them.

In other words, identifying which tissues account for the energy savings tells us about the downstream effectors, but not what the upstream signal is or how it acts. That signal could be neural, humoral, or part of an integrated neuroendocrine pathway. I therefore do not think that tissue-selective metabolic suppression alone argues against a systemic coordinating signal.

2. Recalibration of Thermoregulatory Control Rather Than Simple "Cessation of Defense"

The authors state that torpor requires a "cessation of defense of a minimum Tb of 35 °C." I think this wording may understate how thermoregulation continues to operate during torpor.

Torpor is not simply an uncontrolled fall in body temperature. In hibernators, at sufficiently low ambient temperatures, animals can re-engage metabolic thermogenesis, showing that thermoregulatory control is still present but operating differently. This is also true in mouse FIT. Mathematical modeling of thermoregulation during mouse FIT also suggests that the major change is a marked reduction in thermogenic feedback sensitivity—that is, how strongly the animal responds when body temperature deviates from the theoretical set-point temperature—rather than a complete loss of thermoregulation (Sunagawa and Takahashi, 2016).

I therefore think it would be more accurate to describe mouse torpor entry as a regulated recalibration of thermoregulatory control, rather than simply as a cessation of temperature defense at 35 °C.

3. Temperature-Independent Physiology Beyond the Dominant Contributors to Whole-Body VO2

The manuscript understandably focuses on tissues that contribute substantially to resting whole-body metabolism, such as skeletal muscle, the heart, and BAT. This is reasonable when the goal is to explain whole-body VO2. However, it may miss important physiological changes in organs that make a smaller contribution to total oxygen consumption.

For example, in Q neurons–induced hypometabolism (QIH), protection against ischemia-reperfusion kidney injury persists even when normothermia is experimentally maintained (Kyo et al., 2022). This suggests that at least some biologically important effects of a torpor-like state can occur independently of hypothermia and therefore cannot be explained only by passive Q10 effects.

The mechanism behind this protection is still unclear. It could involve cellular metabolic suppression, altered perfusion, neuroendocrine signaling, immune modulation, or other mechanisms. My point here is not that QIH and natural FIT are equivalent. As the authors also note, they are not. Rather, this finding suggests that it may be premature to assume, based only on whole-body energy accounting, that organs with a smaller contribution to VO2 are simply passive thermal passengers during torpor.

Conclusion:

Overall, I think the quantitative analysis is useful and provides a clear way to explain much of the reduction in whole-body VO2 during mouse torpor. However, I do not think that this calculation alone shows that an upstream coordinating mechanism is unnecessary.

An organ-level energy budget and an upstream neural, humoral, or neuroendocrine regulator address different questions and are not mutually exclusive.

I therefore suggest that the authors distinguish more clearly between two ideas: a factor that directly suppresses metabolism across many or all tissues, and a coordinating mechanism that acts selectively on particular tissues or physiological processes. These are not the same hypothesis. In my view, the current analysis argues more directly against the need for a universal metabolic suppressor than against the existence of an upstream coordinating signal. Moderating the broader claim that a “master mediator” is unnecessary would strengthen the central quantitative argument.

Is the topic of the review discussed comprehensively in the context of the current literature?
Yes

Are all factual statements correct and adequately supported by citations?
Yes

Is the review written in accessible language?
Yes

Are the conclusions drawn appropriate in the context of the current research literature?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Hibernation biology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 25 September 2026

https://doi.org/10.21956/wellcomeopenres.30285.r166534

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Matthew D. Regan
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This was an enjoyable and thought-provoking article. It raises an interesting idea with relevance both to our understanding of torpor and its evolution among the diverse animal groups that use it, and to efforts towards inducing torpor-like states (synthetic torpor) in animals that have not evolved to use it (or, have secondarily lost their ability to use it).

Here are some ideas that came to me while reading the article. They are not really suggestions for how the paper might be improved (it's already published, after all); rather, they are comments to provoke thought and discussion among the authors and any torpor enthusiasts reading the article.

- I was hoping for a little more rigour with the calculations. They are essentially summed estimates of energetic savings, each with sufficiently large margins of error that the summed total can't help but land somewhere near the 75-80% "target". However, while the quantitative precision may be a bit limited, the general idea that a cellular-level metabolic switch is unnecessary in daily torpor is still sound. I'm actually surprised no one has bothered to calculate this before. Maybe they have?
- The authors use the term "master off switch" to describe the process by which individual cells induce an "active" metabolic depression in, say, hibernating mammals. However, I think that what they're putting forward here – that a single process (i.e., the abandonment of 37C Tb) explains the "lion's share" of torpor's energetic savings – actually *is* a master switch, the equivalent of heading into the basement to cut power to the whole house at the breaker instead of turning lights off individually in each room. Anyway, the use of "master off switch" for this or that scenario is semantics and not all that important, but it does underscore an important idea – how a single, central process can instigate metabolic depression in cells across the entire body (in endotherms).
- I fully agree with the authors' interpretation of the VO2-before-Tb sequencing at torpor onset. This is often presented as proof of torpor starting with an active, temperature-independent metabolic depression at the level of the cells, but it's also exactly what a "temperature-first" scenario would look like in an endothermic heterotherm. I feel that this is important, especially in the context of efforts towards translating this type of metabolic plasticity to humans.
- When the authors sum the energetic savings associated with fasting, sleep, zero activity, and Tb reductions from 36 to 26C, they arrive at a total savings of 75-80%, closely matching what is observed in torpid mice. These same factors are also present in the deep hibernators mentioned by the authors. The additional energetic savings observd in such species (~95% vs. 75-80%) are presented as potential evidence for an additional temperature-independent, cell-level metabolic depression mechanism. This may be true, and the authors present some ideas from the literature to support this. However, what is also true is that small hibernators like ground squirrels experience much deeper Tb reductions – to ~5C in 13-lined ground squirrels and as low as -2.9C in arctic ground squirrels (though, at these sub-zero Tb's, the arctic ground squirrels are usually fighting steep thermal gradients in their ~ -20C burrows to maintain even -2.9C). If the authors were to have kept going and extrapolated their Q10's to, say, 5C, would they have arrived near the 13-lined ground squirrel's 95%? It seems close to me! In which case, is it possible that a cell-level metabolic regulator doesn't exist in hibernators either? There's evidence for one, of course, particularly with bears as the authors point out. But in the ground squirrels, could

these pieces of evidence (e.g., PTMs of mito complexes) be consequences, not causes, of cellular metabolic depression? And/or, could they be attributable to some of the higher-level factors mentioned here that contribute to early energetic savings in mice, such as feeding cessation, movement cessation, sleep, etc? I don't know. It seems that high-resolution sampling could be helpful here.

- More broadly, if this strategy is as physiologically straightforward as it seems, then I wonder why more endothermic animals don't use torpor (or at least small-bodied endotherms with high SA:Vs). Maybe they do? And on the other side of the coin, I wonder why hibernators bother with the extra complexity of a cell-level metabolic depressor. Maybe they don't? These seem like potentially useful evolutionary and mechanistic questions to ask.
- The article's framework is quite relevant to synthetic torpor, as the current approaches for this often rely on altering thermogenesis via central activation. If a substantial fraction of the resulting metabolic depression arises due to temperature effects, then an interesting question is whether variation in Q10 among enzymes and physiological processes could ultimately limit torpor sustainability. For eg, as temp falls, perhaps different biochemical pathways will slow at different rates, progressively leading towards some mismatch or other that ultimately constrains torpor depth and/or duration. This idea could be relevant to natural and synthetic torpor.

Is the topic of the review discussed comprehensively in the context of the current literature?

Yes

Are all factual statements correct and adequately supported by citations?

Yes

Is the review written in accessible language?

Yes

Are the conclusions drawn appropriate in the context of the current research literature?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Hibernation metabolism and physiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 15 September 2026

https://doi.org/10.21956/wellcomeopenres.30285.r166530

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Matteo Cerri
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I found this review engaging and thought-provoking. Its principal strength is that it stimulates discussion of the physiological sequence underlying torpor entry and maintenance. The authors propose that centrally coordinated reductions in energetically demanding functions, followed by the temperature-dependent slowing of cellular processes, may account for the metabolic depression observed during fasting-induced daily torpor in mice. This is a valuable hypothesis because it challenges the perceived necessity of a dedicated systemic metabolic suppressor and encourages a more explicit examination of the mechanisms responsible for each phase of the response.

A particularly useful distinction is that a reduction in metabolic rate preceding the fall in body temperature does not, by itself, establish the involvement of a generalized inhibition of cellular metabolism. Selective suppression of thermogenesis and other energy-consuming functions could also produce this sequence. The proposed framework therefore provides a constructive basis for debate between different interpretations of “active metabolic suppression.” I would nevertheless encourage the authors to distinguish consistently between demonstrating that a systemic suppressor is not required to explain the available observations and demonstrating that such a mechanism does not contribute. Framing the proposal as a testable hypothesis, with explicit predictions that distinguish these possibilities, would further strengthen the review.

The scope of the argument should also remain clearly defined throughout the manuscript: it primarily concerns fasting-induced daily torpor in mice under relatively cool ambient conditions. Its applicability to other forms of torpor, seasonal hibernation, or synthetic torpor requires separate evaluation, particularly where body size, thermal inertia, and the relationship between metabolic rate and body temperature differ substantially. Within this scope, I regard the review as a valuable contribution. Its merit lies in prompting the field to clarify which mechanisms are necessary, which are sufficient, and which remain unresolved in the fundamental dynamics of torpor.

Is the topic of the review discussed comprehensively in the context of the current literature?
Yes

Are all factual statements correct and adequately supported by citations?
Yes

Is the review written in accessible language?
Yes

Are the conclusions drawn appropriate in the context of the current research literature?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Physiology of torpor and synthetic torpor.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.