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Understanding the scientific validity of synthetic torpor for radiation research and extended space missions

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The idea of synthetic torpor, an artificial state resembling the hypo-metabolic state of torpor/hibernation, has recently gained significant scientific attention. Building on pioneering research demonstrating the protective effects of torpor against radiation in mammals, this mini-review aims to evaluate its scientific validity. We will explore the theoretical foundations, practical applications, and potential challenges linked to synthetic torpor. By critically examining the current knowledge, we aim to determine if synthetic torpor is a scientifically viable and achievable concept with broad implications for fields such as space exploration and healthcare.

KEYWORDS

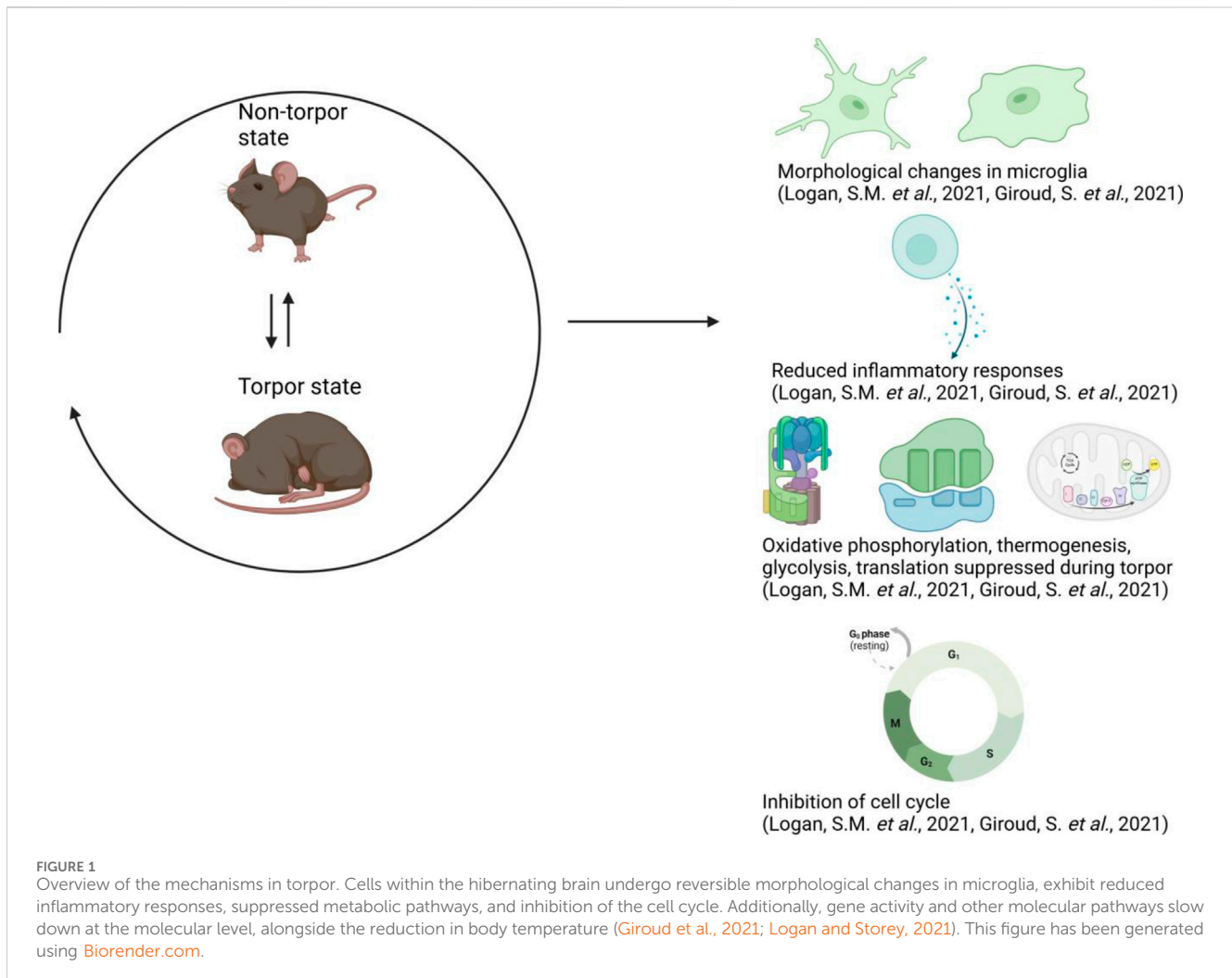
synthetic torpor, radiation, space radiation, hibernation, torpor, hypothermia

1 Introduction

In recent years, research into the mechanism of torpor and hibernation has gained momentum (Hitrec et al., 2019; Hrvatin et al., 2020; Takahashi et al., 2020). Torpor is a state used by some mammals to survive harsh conditions, and avoid predation, and is characterized by a significant decrease in metabolic rate and body temperature (Geiser, 2013; Ruf and Bieber, 2023). A sequence of torpor bouts separated by brief interbout arousals identifies hibernation. During torpor/hibernation, all physiological systems have to adapt to the new condition of low metabolism, and many of these adaptations offer interesting opportunities for medical (Cerri, 2017) and space technology (Choukér et al., 2021; Cerri et al., 2021).

In the last decade, a few procedures have been shown to be effective in mimicking torpor in non-hibernating mammals—a state referred to as synthetic torpor—garnering significant attention in the realms of space and medical research (Cerri et al., 2013; Takahashi et al., 2020; Tupone et al., 2013; Yang et al., 2023; Zakharaeva et al., 2019; Squire et al., 2020). As the scientific community investigates the fundamental mechanisms of torpor, questions about the potential applications of synthetic torpor, its scientific validity and its broader applicability become increasingly relevant.

Our goal is to scrutinize the scientific underpinnings, practical implications, and potential challenges associated with synthetic torpor. By evaluating its potential across



diverse fields such as space exploration and healthcare, we aim to determine whether this concept holds genuine scientific promise or remains an aspirational idea with substantial obstacles yet to overcome. In doing so, we aim to contribute to the ongoing discussion on the validity and feasibility of synthetic torpor in the context of future scientific advancements.

2 Historical background

Torpor has garnered global attention due to its recently suggested applications for space exploration and medical interventions (Petit *et al.*, 2018). Despite its promise, the true power of torpor remains largely untapped, primarily because the underlying mechanisms of this behavior have yet to be fully understood. While scientists have made efforts to comprehend the natural hibernation processes of animals, the current surge in interest centers around the induction of synthetic torpor through pharmaceuticals (Schafer, 2023). Replicating the natural hibernation process using chemicals and drugs presents a promising avenue for pharmacological development.

Overall, two main uses of synthetic torpor can be envisioned: the first one is to replicate the entire behavior, exploiting the full

set of physiological adaptations; the second one is to understand the mechanism of single system/organ adaptations to develop specific medical treatments or countermeasures for space exploration. Among these, a particularly interesting case is the resistance to radiation damage induced by torpor (Cerrri *et al.*, 2016; Puspitasari *et al.*, 2021). Metabolic rate was first hypothesized to modulate radiation resistance when patients treated with the available thyroid hormone reported higher sensitivity to radiation (Smith and Smith, 1951). If higher metabolism was sensitized to radiation damage, hypometabolism might have been protective. Since torpor and hibernation are the natural models with the largest decrease in metabolic rate, squirrels and other hibernators were tested for their response to radiation exposure (Musacchia and Barr, 1968). The results indicated that torpor was indeed protective against the damage induced by radiation. When procedures for synthetic torpor were later developed, it was only natural to test if this pharmacologically induced state shared such features with natural torpor (Puspitasari *et al.*, 2022).

Research on various hibernating animals, such as ground squirrels, bears, and certain bat species, has contributed to our understanding of the physiological and biochemical mechanisms of adaptation. These studies have provided a first frame to

understand the physiology of torpor, as described in (Figure 1) (Andrews, 2007; Neff, 2018). This mechanism enables small mammals not only to endure periods of low resource availability or high energy demand but also to tolerate increased competition with other species for limited resources (Levy et al., 2011; Heldmaier and Steinlechner, 1981). Numerous physiological changes have been observed during torpor and hibernation, including very little muscle loss despite prolonged periods of immobility, alterations in immune cells reactivity (including those in the gut), changes in the physiology of the gastrointestinal tract (GI tract) (Sisa et al., 2017; Regan et al., 2022; Carey and Assadi-Porter, 2017; Greene et al., 2022), neuroinflammation (Arendt and Bullmann, 2013; Chiocchetti et al., 2021; Hitrec et al., 2021; Luppi et al., 2019; Squarcio et al., 2023), and a decrease in protein synthesis (Wei et al., 2019; Morin and Storey, 2009; Kurtz et al., 2021). Torpor duration can vary significantly: from less than 24 h in species displaying what is called “daily torpor” to several weeks in species undergoing seasonal hibernation, in which sequential torpor episodes are separated by 24 h interbout arousals.

Recently, studies using mostly animal models for daily torpor, such as mice, have unraveled the neural network responsible for natural torpor, in the attempt to better understand the process and build the knowledge required to replicate it in non-hibernators (Ambler et al., 2022; Hitrec et al., 2019; Hrvatin et al., 2020; Takahashi et al., 2020; Yamaguchi et al., 2023). These studies show that VGLUT2- or Adcyap1-positive neurons within the avMLPA appear to be responsible for the induction of torpor (Hrvatin et al., 2020; Takahashi et al., 2020). The involvement of the hypothalamus is also supported by the findings that there is an upregulation of thioredoxin-interacting protein (TXNIP) in the hypothalamus, all influenced by factors such as food and water consumption (Hand et al., 2013).

3 The science of synthetic torpor and scientific validity

Several procedures, such as the use of pharmacology and ultrasound, have been shown to be effective in inducing a state of synthetic torpor in rats, which are used as non-hibernating animal model (Takahashi et al., 2020; Cerri et al., 2013; Tupone et al., 2013; Yang et al., 2023; Zakharova et al., 2019; Zakharova et al., 2021). Previous work highlights the role of hydrogen sulfide (H₂S) in mimicking torpor in mice by suppressing mitochondrial respiration during torpor (Haouzi et al., 2008). However, we must take into account that mice are known as animals that can go into torpor naturally. Mice exhibited a 90% reduction in metabolic rate with (H₂S) at 80 ppm and 17% oxygen (Haouzi et al., 2008; Jensen and Fago, 2021). Despite the positive results in mice (H₂S), was not effective in inducing torpor in non-hibernating species (Haouzi et al., 2008; Drabek et al., 2011).

The first effective procedure to induce synthetic torpor in non-hibernating animals were first shown by repeated injections of the GABA-A agonist muscimol into the Raphe pallidus (RPa) region. RPa is a key thermoregulatory region within the brainstem; RPa neurons stimulate thermogenesis when activated and thermal dissipation when inhibited (Cerri et al.,

2010; Morrison and Nakamura, 2019). The results showed that prolonged RPa inhibition resulted in deep hypothermia, accompanied by a decreased heart rate and EEG activity, which are similar to natural torpor animals (Cerri et al., 2013).

Other research on rats has suggested that synthetic torpor can be induced through the injection of adenosine agonist such as 5'-Adenosine monophosphate (5'-AMP), which activates central adenosine (A1) receptors (A1ARs) (Tupone et al., 2013; Iliff and Swoap, 2012; Shimaoka et al., 2018; Jinka et al., 2011), a pharmacological intervention effective also on mice (Ghosh et al., 2017; Silvani et al., 2018). Activation of A1ARs in rats led to a torpor-like state and reduced body temperature, possibly associated with the inhibition of brown adipose tissue (Tupone et al., 2013). Moreover, 5'-AMP has shown to protect both mice and rats against total body irradiation (TBI) from X-rays and has also found on rats following TBI with heavy ions (Ghosh et al., 2017; Puspitasari et al., 2022; Tinganelli et al., 2019). While radiation resistance seems to be present in both natural and synthetic torpor, other physiological functions, such as mitochondrial function have been shown to differ (Sgarbi et al., 2022).

Another promising approach to induce a torpor-like state is through remote transcranial ultrasound stimulation targeted at the hypothalamic preoptic area (POA). This noninvasive, precise, and safe method achieves a long-lasting (> 24 h) torpor-like hypothermic and hypometabolic state in rodents. By employing closed-loop feedback control of ultrasound stimulation with automated detection of body temperature, ultrasound-induced hypothermia and hypometabolism (UIH) is triggered by the activation of POA neurons, involving the dorsomedial hypothalamus as a downstream region and subsequent inhibition of thermogenic brown adipose tissue. Single-nucleus RNA sequencing of POA neurons has identified TRPM2 as an ultrasound-sensitive ion channel, the knockdown of which suppresses UIH. Notably, this method has also demonstrated feasibility in non-torpid animals, such as rats. The UIH is a potentially promising technology for the noninvasive and safe induction of a torpor-like state (Yang et al., 2023). These advancements suggest that synthetic torpor could be a valuable tool in medical and space-related research, where metabolic reduction and survival under extreme conditions are crucial. However, further studies are necessary to optimize these techniques and fully understand the underlying mechanisms involved.

4 Applications and technological challenges

The induction of torpor in animals offers potential benefits, as demonstrated by Weissman et al., who provided proof-of-concept evidence for its benefits in long-duration space missions (Weissman et al., 2024). Torpor induces a hypothermic, hypoactive, and hypometabolic state that activates multiple biological countermeasures to the conditions encountered in space missions (Choukér et al., 2021; Pavez et al., 2021; Cerri, 2017). Nevertheless, translating this to humans presents significant challenges (Griko and Regan, 2018). Some studies and technologies already exist for implementing hypothermia in cardiac arrest patients, such as in the study

referenced (Dankiewicz et al., 2021). However, the process of inducing hypothermia differs from torpor, which not only requires hypothermia but also coordination with other physiological processes and functions (Geiser et al., 2014). Moreover, these studies focus specifically on patients who have experienced cardiac arrest and not on healthy subject.

The idea of implementing torpor in space missions could yield cost-efficiency benefits, with astronauts consuming less oxygen, food, and water, and protecting against cosmic radiation (Shi et al., 2021). Additionally, it may help mitigate muscle tissue loss, a common issue in long-space flights, and provide protection from harmful cosmic radiation damage (Cerri, 2017; Puspitasari et al., 2021). Torpor's ability to reduce the impact of environmental stressors, such as confinement, and it could help preserve neuroendocrine and immune systems during missions (Nordeen and Martin, 2019; Crucian et al., 2014). Apart for Beyond Low Earth Orbit (BLEO) space exploration, torpor is thought to be a promise in cancer treatment by slowing tumor progression through metabolic depression (Schafer, 2023). Studies on hamsters with sarcomas has shown that tumor growth can be halted during hibernation (Lyman and Fawcett, 1954).

The induction of synthetic hibernation for space travel in astronauts is a fascinating concept, yet it remains under discussion, as torpor induction studies in mammals are still in early stages. NASA's Phase I study showed that subjects could be kept in a mild hypometabolic state for up to 14 days without fatal outcomes, suggesting the potential of induced hypothermia in humans (Nordeen and Martin, 2019). Hypothermia one of the primary physiological changes in torpor, is commonly employed for cardiac arrest patients. Studies have demonstrated that humans can achieve mild hypothermia (35°C–36.3°C) for approximately 90 min through intravenous dexmedetomidine administration (Callaway et al., 2015). However, this duration is inadequate for long-term space travel, and extended hypothermia beyond 24 h raises risks of immune and gastrointestinal issues (Shi et al., 2021). Ongoing research is exploring the role of the CNS in regulating torpor and the mechanisms for inducing this state in humans. Moreover, as mentioned earlier in this review, hibernation might help mitigate the adverse effects of radiation exposure in space (Shi et al., 2021). In the context of cancer treatment, radiotherapy, either used alone or in combination with chemotherapy, is limited by the maximum tolerable dose for each organ (Shi et al., 2021). Exploring how synthetic hibernation influences radioresistance in both normal and tumor tissues could be intriguing, as it may play a significant role in halting tumor growth.

4.1 The future of synthetic torpor research and its potential impact

While there's been some success in inducing torpor artificially, scientists still have concerns about its safety, how well induction methods work, controlling how long it lasts, whether it is truly like natural torpor, whether it can be reversed, potential risks, if it applies to humans, and its long-term effects on health and behavior. These concerns revolve around the effectiveness of torpor induction methods, the ability to replicate all the features of natural torpor states, and the potential risks and long-term consequences.

Therefore, scientists must continue refining the process to improve its quality and safety. Key challenges include:

- Extending synthetic hibernation to last for days or months;
- Optimizing pharmacological protocols to simplify and more accurately replicate natural hibernation;
- Understanding the long-term risks associated with synthetic hibernation;
- Ultimately translating the procedure for use in humans.

It has been suggested that metabolic depression is similar to torpor. Achieving shallow metabolic depression (20% reduction of metabolic rate relative to basal levels) is a feasible first step towards synthetic torpor during human spaceflight. This could potentially benefit crew health, reduce spacecraft demands, and serve as a testbed for deeper metabolic depression technologies. The benefits of shallow metabolic depression would include increasing sleep time to 7–8 h per night, which might reduce life support system requirements and decrease caloric needs (Regan et al., 2020).

Moreover, the study in rats has shown that synthetic torpor triggers a neuroprotective effect on the brain, reversing brain Tau hyperphosphorylation. This might open new paths to study the treatment of Alzheimer's and other associated diseases (Squarcio et al., 2023).

5 Conclusion

This review provides a concise analysis of synthetic torpor, emphasizing its significance in both clinical and space research, while also illuminating the challenges that may arise. In nature, hibernation is a seasonal adaptation associated with low body temperature and driven by environmental changes. Cerri et al. first introduced the term 'synthetic torpor,' defining it as a state of artificially induced reversible metabolic depression (Cerri, 2017). Synthetic torpor could be induced by clinical drugs such as 5'-AMP, leading to a decrease in body temperature and metabolic rate. Since torpor is associated with many physiological changes, it could also increase the survival probability of patients in life-threatening conditions by slowing metabolism and disease progression (Hypothermia after Cardiac Arrest Study Group, 2002).

Previously, we have proposed the idea of possible synthetic torpor for space travel (Cerri et al., 2016), (Puspitasari et al., 2021). In this review, we consolidate recent findings from animal models to establish a foundation for future studies and identify key areas for further research to bridge the gap toward human application. Despite the challenges associated with torpor, there is increasing evidence that its use could be advantageous from both clinical and scientific perspectives, especially for long-duration space missions. Interestingly, torpor provides space-protective effects to the body, including the preservation of muscle and bone mineralization, as well as radiation resistance. However, studies on synthetic torpor's ability to reduce radiation effects have so far been limited to rodent models, and significant challenges remain before this approach can be applied to humans.

In the area of synthetic torpor, much remains to be explored, and torpor-inspired technologies are still in their infancy. Nevertheless, with adequate support from government agencies, private biotech

firms, and biomedical companies, the development of highly beneficial torpor technology could be within reach for this generation.

Author contributions

AK: Writing—original draft, Writing - review and editing. RC: Writing—review and editing. KS: Writing—review and editing. MC: Writing—review and editing. WT: Writing—review and editing.

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