Timeout with Torpor:
History, Biology, and Future Medical Applications of a Survival Strategy

by

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SUMMARY

As human lifespans increase, technological advances push forward to continue this trend, and human torpor has entered the discussion as a mode to improve longevity, especially by reducing patient mortality. The purpose of this paper is to synthesize literature regarding humanity's history with hibernation, to discuss potential methods to induce torpor in humans, and to determine if there may be an ethical future for this historical survival mechanism in modern medicine to increase patient longevity. Recent, historical, scholarly, and popular media were synthesized to gain background and address this research focus. Ultimately, this paper concludes that there is evidence associating hibernation with comparatively greater longevity in mammals, and humans may be able to trigger their dormant torpor gene. With several potential methods to synthetically induce torpor underway, particularly paired with hypothermic temperature manipulation, and a renewed interest that led to increased funding for human torpor-related projects, we may see the medical future of torpor as a treatment for diseases such as cancer and method of preservation for patients in critical condition within this lifetime. However, there are many questions regarding the ethics of the future practice that remain unanswered until it reaches further development.

Key words: *torpor*, *hibernation*, *metabolic rate depression*, *hypothermia*, *synthetic torpor*

INTRODUCTION

Hibernating animals share many health benefits that are correlated to metabolic rate depression in stressful conditions compared to their non-hibernating relatives, such as longer lifespans and reduced instances of age-related diseases (Al-attar and Storey 2020, Pinho et al. 2022). Hibernators also have greater control over their endocrine system, which has implications for treating metabolic diseases such as diabetes, among others (Wu et al. 2013). Torpor, a specific type of metabolic rate depression akin to hibernation, has gained traction more recently among scientists, particularly regarding applications in space exploration and medicine (Bloomberg Quicktake contributors 2022). While humans possess the dormant torpor gene, we need to find methods to imitate natural torpor to allow for future medical applications (Cerri 2016). Thus, many avenues are underway to induce synthetic torpor, especially through chemical pathways (Jensen and Fago 2021, Pan 2018). It is apparent that low temperature is important, if not necessary, to induce and maintain a torpid state but may induce hypothermia without a chemical control component (Wu et al. 2007).

Discussions about human hibernation can be traced back to centuries-old stories around the globe utilizing the "suspended animation" technique, which is best described as an ageless sleep which allows characters to skip years of time unscathed (The Encyclopedia of Science Fiction contributors 2016). These stories manifested into reality, evidenced by several instances across history, including both intentional and accidental employment of torpor-like states by people and pre-human sapiens for survival, suggesting the ability to enter torpor may be preserved in some people (British Medical Journal contributors 2000, MacDonald 2014, Ortiz 2015). Considering our ancestors and icy accidents as recently as 2015, finding ways to induce, control, and use torpor as a medical advancement may come sooner than expected, but (Ortiz 2015). Here, I assemble and discuss the scientific background, history with roots in mythology, and accidental incidents, so future researchers can advance the discipline.

BACKGROUND

Terminology

Myriad animal species have a mechanism known as metabolic rate depression, which shuts down excess biological processes in stressful environments to conserve energy (Mohr et al. 2020, Al-attar and Storey 2020). The process generally works by retaining essential cellular processes, such as cytoprotective and anti-apoptotic responses, while less important, energy-expensive, and sometimes harmful mechanisms, including apoptosis and cell division cycles, are significantly reduced (Al-attar and Storey 2020). This process occurs due to the importance of homeostasis, the balance between energy input and output, to cells. Thus, in response to harsh conditions such as frigid weather and low food reserves, the animal enters a state of "suspended animation," the most commonly-known of which is hibernation (Mohr et al. 2020). Hibernation is a "deep torpor," where many back-to-back cycles of torpor lasting less than 24 hours accumulate to allow the animal to stay in a dormant state for weeks on end with short normothermic

states interspersed (Bouma et al. 2011). In torpor, cell function is significantly stalled; it neither repairs itself nor dies as fast as usual, and resource consumption including that of oxygen is limited (Quinones et al. 2014). Moreover, evidence suggests this state is primarily induced in mammals once their core temperature drops below 31 centigrade, or, in other words, in hypothermic conditions (Lee 2008). Torpor is naturally induced by genetic, circadian, and ambient factors, all of which are controlled by pathways in the central nervous system, as shown in Figure 1 (Cerri 2016). Torpor is not a restful state in that it requires animals to recover afterward; however, its effects on metabolic rate may allow for improved medical care by slowing the progression of cell-related diseases (Bloomberg Quicktake contributors 2022).

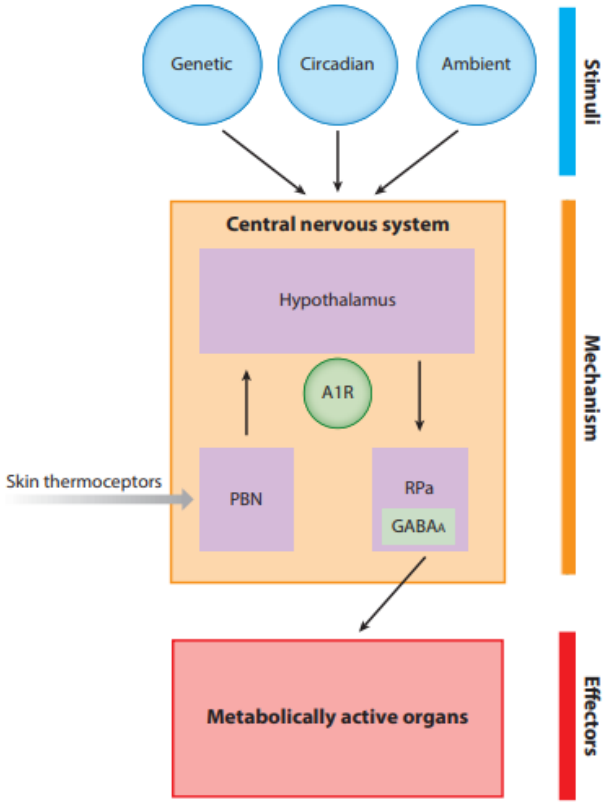

Figure 1. A simple schematic of torpor induction, depicting the pathway from general stimuli to skin receptors, which are sent through the parabrachial nucleus (PBN) to the hypothalamus, and eventually arrive at the organs via the raphe pallidus (RPa). internal mechanisms including the parabrachial nucleus (PBN) (Source: Cerri 2016).

While some sources use torpor and hypothermia interchangeably, researchers have found fundamental distinctions to differentiate the two. For example, clinical hypothermia refers to an uncontrolled state in which core body temperature cools due to low ambient temperatures in environments or other factors that interfere with thermoregulation and homeostasis (Geiser et al. 2014). This definition is like that of torpor; however, the key descriptor is "uncontrolled state" which does not apply to torpor,

according to evidence that torpor is endogenously regulated at every point during the cooling and warming periods, whereas hypothermia does not show the same endogenous functions. Additionally, hypothermia and torpor are fundamentally different in animals that naturally hibernate. They have reverse effects on metabolic rate and core temperature cooling rates when induced separately in juvenile rats: torpor resulted in rapid cooling at first that slowed to reach a plateau, whereas hypothermic conditions resulted in slow cooling that later sped up until core temperature dropped below 20 centigrade (Geiser et al. 2014). However, the term hypothermia may generally refer to a reduction in core body temperature, and thus can be applied to the concept of torpor (Mohr et al. 2020).

Torpor Biology

Since humans have evolutionarily lost the ability to hibernate, understanding the biological and chemical elements of natural hibernation is essential to developing successful synthetic conditions (Cerri 2016). Hibernation generally occurs during the cold, dark winter. These factors result in biological changes, such as neurological signals from increased darkness that alter circadian rhythm in response to reduced photoperiod, and increased metabolic costs for endothermic animals (Studd et al. 2021). In naturally-hibernating mammals, overall activity, including heart rate, respiration activity, and blood pressure are all significantly reduced (Mohr et al. 2020). Despite these changes that would normally cause organ damage in non-hibernating, homeothermic mammals, natural hibernators wake up unscathed due to several factors, some of which are understood but many are still unknown (Mohr et al. 2020).

Recent research has uncovered hydrogen sulfide (H_2S) as a key signaling molecule to maintain torpid states (Jensen and Fago 2021, Pan 2018). Mice boast a 90% reduction in metabolic rate with H_2S at 80ppm and 17% oxygen (Cerri 2016). Studies on the administration of H_2S to induce torpor led to further research on its endogenous levels in natural hibernators, which found that the synthesis of H_2S increases in torpid states (Jensen and Fago 2021). In a study on the effect of hydrogen sulfide ion (HS^-) concentrations on neutrophils, it was found that a dose of 0.50 ± 0.12mM inhibited neutrophil apoptosis by half (Rinaldi et al. 2006). Other studies corroborate this and the indication that H_2S reduces inflammation (Jensen and Fago 2021). The use of H_2S will be discussed further as a method to synthetically induce torpor in non-hibernating species. Other biological responses to reduce damage include reduced blood clotting factors prevent stroke or pulmonary embolism as a result of slowed blood flow (Pan 2018).

Despite numerous mechanisms in place to reduce damage during torpor, intermittent arousal is essential to resume essential functions like transcription and translation throughout the hibernation cycle (Mohr et al. 2020). Intermittent arousal refers to the state when core body temperature reaches normothermic levels, demonstrated in Figure 1, and allows the resumption of cell transcription and translation to produce replacement proteins that were damaged during torpor, immune system stimulation, restful sleep, and cellular waste removal (Mohr et al. 2020). Since arousal from torpor is necessary for restful sleep, this corroborates the assertion that torpor is a

stressful survival state which requires recovery periods. Awareness of intermittent arousal in the hibernation cycle provides a greater understanding of the potential successes and limitations of torpor applications in medicine, which will be explored further.

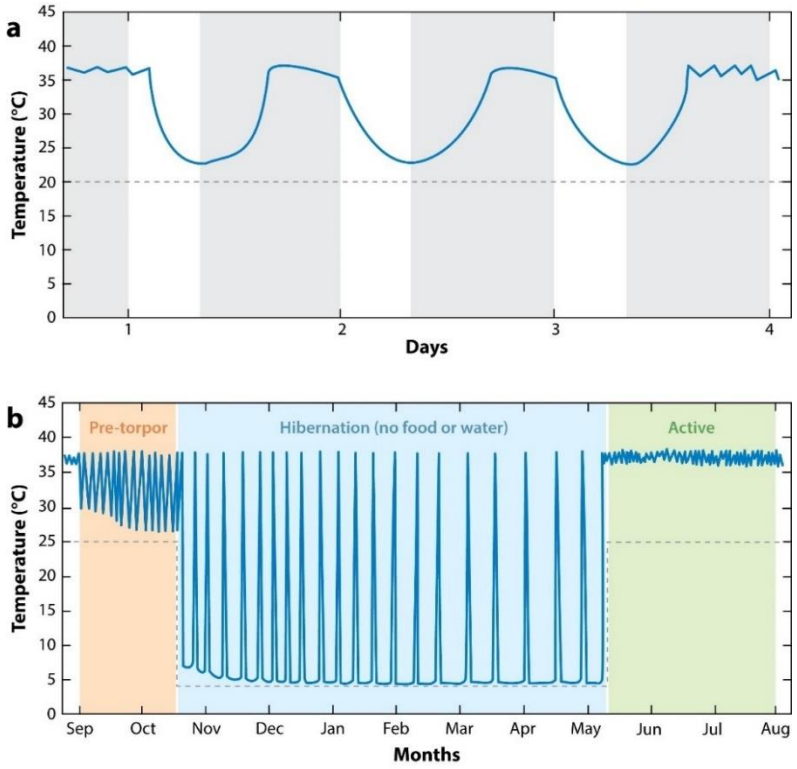

Figure 1: Schematic of core body temperature of (a) a daily heterotherm undergoing daily torpor bouts and (b) an obligatory hibernator demonstrating seasonal hibernation. The gray dashed lines represent room temperature (Source: Mohr et al. 2020).

HISTORY

Mythology

Human hibernation has long intrigued humans throughout history and has been featured in many stories and mythologies (Geiser et al. 2014). In many cultures across the globe, there are examples of stories where a character enters a long sleep and emerges not only unscathed but often untouched by time. This plot device, often referred to as "suspended animation" or the "sleeper awakes" device in literature become a staple in science fiction in the 19th century but has been known in mythology for centuries (The Encyclopedia of Science Fiction contributors 2016). Popular Western examples of stories that use this device include *Sleeping Beauty* and *Rip van Winkle*, the former of which originated in Norse mythology and continued its adaptation throughout history (Bowes 2021). Excerpts of various tales involving Endymion signify that the "suspended animation" device has existed as far back as the 3rd century AD in both ancient Greece and Turkey (Greenberg 2020). Table 1 features a more comprehensive list of suspended animation stories. To this day, movies across genres, like 2016's sci-fi film *Passengers* and 2015's

romance *The Age of Adaline* employ suspended animation as a plot device to transport characters safely through long periods of time, ageless and unscathed.

Table 1: Historical myths and stories related to human hibernation or suspended animation

Story	Description
Endymion	From Ancient Greece and Turkey, originating in the 3rd century, this myth follows a man who falls in love with the moon goddess and is put in an eternal sleep, where he maintains his youth is consistent across all (Source: Greenberg 2020).
Sigurd and Brunhild	A 5th century Norse mythological tale, this story is about Brunhild the Valkyrie who is put into a magical sleep by Odin after defying him in battle. After a long time, Sigurd rescues her from slumber (Source: World Book 2017).
Zhang Yunrong	From 9th century China, this tale is about Zhang Yunrong, who is given a magical immortality pill by her soon-to-be husband, Xue Zhao and must sleep for 100 years after death, then have intercourse with a living person before the immortality takes effect. Zhang Yunrong and Xue Zhao are said to be alive to this day, still ageless and together (Source: Starostina 2012).
Shen Yuanzhi	From 9th century Chinese tale, this story is similar to *Zhang Yunrong*, where Zhao Yunrong is given a magical pill by the Daoist Shen Yuanzhi for when death is near. Yunrong falls asleep for 100 years before awakening, although mixing "seminal energy" is not required in this version (Source: Starostina 2012).
King Arthur	Originating in 9th century England, this story follows Arthur who united his people and shall remain asleep until a wizard's horn blows, notifying him that England needs him again (Source: Mark 2017, Simpson 1986)
Perceforest	From France, first written in the 1330s or 1450s, Book 3 of this long manuscript features a story about a girl who is cursed to fall into a preserved sleep after pricking her finger on a spindle. Her lover impregnates her, and their child sucks the splinter out, allowing her to wake (Source: Campbell 2013, Cox 1990).
Sun, Moon, and Talia	Written in 1634 Italy, this fairytale details a princess who falls into an enchanted sleep when a splinter of flax embeds in her finger. A king impregnates her during the sleep, and she awakens when one of the babies sucks the splinter out (Source: Ashliman 2013).
The Sleeping Beauty in the Wood	From France, written in 1697, this is a fairytale about a princess cursed by an evil fairy to sleep for a hundred years before being awakened by a handsome prince (Source: Ashliman 2013).
Rip van Winkle	From the United States, written in 1820, this is a story about a man who falls asleep in the mountains and wakes 20 years later as an old man but otherwise unscathed (Source: Irving 1820).

Strategic Torpor

While some scientists agree that the ability to enter torpor has long been lost in humans, others have taken a deeper look into history, particularly at other mammals and sapiens that evolved before humans (Bartsiokas and Arsuaga 2020). Bartsiokas and Arsuaga's study on the remains of pre-human sapiens revealed many bone issues, including "trabecular tunneling and osteitis fibrosa, [...] rachitic osteoplaques and empty gaps between them, craniotabes, and beading," consistent with hibernation's long periods of low activity. The sheer number of issues found in the bones implies hibernation was poorly-tolerated, but its use by these homo sapien relatives may suggest that humans have maintained the genes and physiology to support torpid states (Bartsiokas and Arsuaga 2020). Instances of humans undergoing states of reduced metabolic function, like torpor, in recent history further solidifies this theory.

One of the most prolific examples of humans entering torpor-like states in recent history is outlined in a 2000 article from the British Medical Journal, detailing peasant experiences in the northwestern Russian province, Pskov (British Medical Journal contributors 2000). With an average winter temperature of 18°F, or -8°C, survival was difficult in times before modern heating (Dugbartey et al. 2015). Until about 100 years ago, famished peasants in Pskov functioned in a state very similar to hibernation, called *lotska*, in which they entered daily periods of torpor rather than a single, months-long slumber (British Medical Journal contributors 2000). They would sleep for nearly the entire day, waking only once to check the fire and eat and drink their allotted food of blackened bread and water ration (New York Times 1906). This "pseudo-hibernation" occurred for up to six months each year, after which they emerged to begin their productivity again in the warmer months.

Accidental Torpor

The phrase "not dead until they're warm and dead" originates from Anna Bågenholm's 1999 skiing accident, where she survived record time under frigid water (MacDonald 2014). During the first half of her 80-minute submersion, Bågenholm found an air pocket under the ice and was able to remain conscious, but she soon stopped moving. By the time a rescue team arrived and were able to remove her from the ice, there was no sign of life. She was "frozen solid" and had the lowest body temperature ever recorded in a survivor: 56.7°F (13.7°C) (MacDonald 2014). Her fellow skiers were fortunately doctors who performed CPR over the hour-long helicopter ride to the nearest hospital (Martin 2009). The icy temperatures allowed Bågenholm's metabolism to slow, preserving her organs from irreparable damage despite the long duration without oxygen (MacDonald 2014).

Figure 3: Anna Bågenholm's rescue team treating her after pulling her from the ice (Source: Martin 2009, photo by Ketil Singstad).

Bågenholm's story is consistent with others, including much earlier reports from Napoleonic medics that injured soldiers left in the cold had higher survival and recovery rates than higher-ranking officers allowed to recover in warmed tents (Swain 2014). Furthermore, the 2015 account of St. Louis teen, John Smith, follows a similar trend (Ortiz 2015). Smith fell through ice and was submerged for 15 minutes, initially declared clinically dead when he was pulled out. 45 minutes later, with a body temperature down to 88°F (31°C), Smith awoke with full brain function. Medical personnel concluded that drowning in the icy water worked in the boy's favor, as the core temperature drop put him into a state of torpor that preserved his body from more severe damage, and he made a full recovery (Ortiz 2015). As reports of these incidents and similar others gained traction among the media, greater attention was placed on this biological phenomenon which allows people to make a full recovery from freezing, anoxic conditions that should have otherwise been lethal, propelling contemporary interest in human hibernation research (Bloomberg Quicktake contributors 2022).

SYNTHETIC TORPOR INDUCTION

Chemical Factors

H_2S is endogenously produced in mammals and offers many benefits due to its anti-apoptosis, anti-oxidative, and anti-inflammatory properties that work to preserve cell life and slow down oxidative respiration in mitochondria (Pan 2018). Inhalation of exogenous H_2S can induce torpor in small animals such as mice and Syrian hamsters with a full recovery and no notable side effects (Dugbartey et al. 2015). However, when applied to larger animals such as piglets, H_2S fails to consistently induce a torpid state, but this may be due to a proportionally reduced dose since H_2S is toxic in larger amounts and causes liver damage (Pan 2018). Studies on the use of exogenous H_2S to induce torpor have

offered varied results; thus, it remains inconclusive if this route could actually work as the sole induction method for human torpor (Jensen and Fago 2021). Still, H_2S may be an important aspect of safe entry, maintenance, and arousal from synthetic torpor. There is evidence of increased renal injury among non-hibernating rats during induced torpor without H_2S present and increased survival among mice after hours of O_2 content as low as 3% (Cerri 2016, Dugbartey et al. 2015). H_2S-induced torpor additionally allowed rats' core body temperatures to drop as low as 15 centigrade, succeeded by spontaneous arousal as environmental temperatures increased without any expected hypothermic side effects (Lee 2008).

Rather than focusing on administration of external H_2S, research on increasing chemicals or hormones that are known to enhance endogenous H_2S synthesis, such as nitric oxide and testosterone or AdoMet, which are cystathionine β-synthase up-regulators, could be further explored (Kabil, Vitvitsky and Banerjee 2014). However, researchers should note any prior studies on the effects of these chemicals or hormones on torpor success, considering higher testosterone levels "prevents continued hibernation" and, in high doses, led to a complete inability to enter natural torpor among golden-mantle ground squirrels (Lee et al. 1990, Kucheravy et al. 2021).

Another possibility of chemical induction, and possibly more promising, is via injection of 5'-Adenosine monophosphate (5'-AMP) (Dugbartey et al. 2015). While 5'-AMP is not as clearly understood as H_2S, research by Dugbartey et al. suggests the pathways are similar. The low water solubility of 5'-AMP indicates it may not be the primary activator for natural torpor; however, since synthetic torpor allows prior dissolution in organic solvent, finding and applying entirely natural mechanisms may not be essential (Lee 2008). Still, 5'-AMP does appear to play a role in natural torpor, as a study on naturally-hibernating mice sent into fasting-induced torpor showed significantly raised levels of 5'-AMP in their blood compared to non-hibernating counterparts (Dugbartey et al. 2015). When injected into non-hibernating-mice. 5'-AMP induced a hypothermic state of 25 centigrade body temperature even when situated in normal room temperature surroundings, which the mice arose from without any evidence of organ damage, suggesting the reduced metabolic state induced by 5'-AMP injection activates natural preservation responses in non-hibernating animals (Lee 2008). It is also worth noting that 5'-AMP torpor led to increases in endogenous H_2S (Dugbartey et al. 2015). Other chemical pathways to consider for synthetic torpor induction includes direct inhibition of RPa neurons via microinjections of muscimol, the GABAa receptor agonist, which was the first successful synthetic induction method for a non-naturally-hibernating rat species (Cerri 2016).

Therapeutic Hypothermia

Temperature manipulation has been a promising method thus far of inducing torpor in larger mammals that better simulate humans (Wu et al. 2007). Studies have shown that warming the anterior hypothalamus generally reduces metabolism, while cooling increases it; however, the open loop theory of temperature regulation may

contextualize possible loopholes, where the anterior hypothalamus is only one vector of control but others exist to counteract its effects on metabolic rate (Cerri 2016). While several neural mechanisms related to thermoregulation are understood, how they interact and effect other thermoregulatory circuits is still largely unknown or based in theory, so fully immersing human subjects in temperature-controlled environments to induce torpor is still beyond approval. However, the use of emergency preservation and resuscitation (EPR), in which a hypothermic state is induced in cardiac arrest patients to buy time for proper treatment, has been used successfully on human subjects and offers a good starting point (Kutcher et al. 2016). There is currently an on-going clinical trial on EPR with an estimated primary completion date in December 2023 (ClinicalTrials.gov identifier NCT01042015). The methodology employed in this trial involves rapid cooling of trauma victims experiencing cardiac arrest by pumping ice-cold saline solution through their descending thoracic aorta, resulting in a brain temperature of ‹10°C that is maintained for one hour. The goal of this study is to increase survival from the initial injury while minimizing potential neurological damage from the sustained hypothermia.

One likely reason that the clinical trial limits the cooled state to one hour is because hypothermic conditions lasting longer than two hours could result in loss of brain function or a persistent comatose state, so caution must be observed when using these preservation techniques (Wu et al. 2007). The addition of oxygen and glucose to the saline flush was shown to extend the time before onset of neurological damage to three hours in dogs suffering cardiac arrest (Wu et al. 2007). If the addition of nutrients such as oxygen and glucose can extend this "safe" period by an hour, it could be possible that the addition of inflammatory, metabolic, and/or oxidative inhibitors such as 5'-AMP or a different agent could extend it even further by allowing a hypothermic state to transition into a preservative torpid state.

MEDICAL APPLICATIONS

Longevity Improvements

Researchers have yet to identify the causes of aging or why biological age does not always align with chronology in some individuals, based on wide variation in biological risks among a group of same-age individuals (Pinho et al., 2022). Due to this, researchers have been in the process of finding and developing biomarkers for aging, one of which is based on chronological aging regressed on DNA methylation called epigenetic clocks (Pinho et al., 2022). Hibernation appears to increase lifespan, according to studies on epigenetic aging. A study on hibernating marmots indicates that their epigenetic aging slows during periods of torpor but returns to a normal rate during times of animation. Figure 2 illustrates epigenetic aging rates based on the Epigenetic Pacemaker (EPM) model, which has a median absolute deviation of 0.899 (Pinho et al. 2022). Furthermore, many hibernating mammals live significantly longer than similar-sized, non-hibernating relatives: hibernating grey mouse lemurs outlive house mice by several years (Al-attar and Storey 2020). Some hibernators boast lifespans as much as 10 times longer than what is estimated based on their size, such as Brandt's bats, *Myotis brandtii*. Age-associated diseases

such as Alzheimer's may also be implicated in relation to the longevity effects of hibernation, suggesting torpor may prevent or slow the onset of such diseases (Al-attar and Storey 2020).

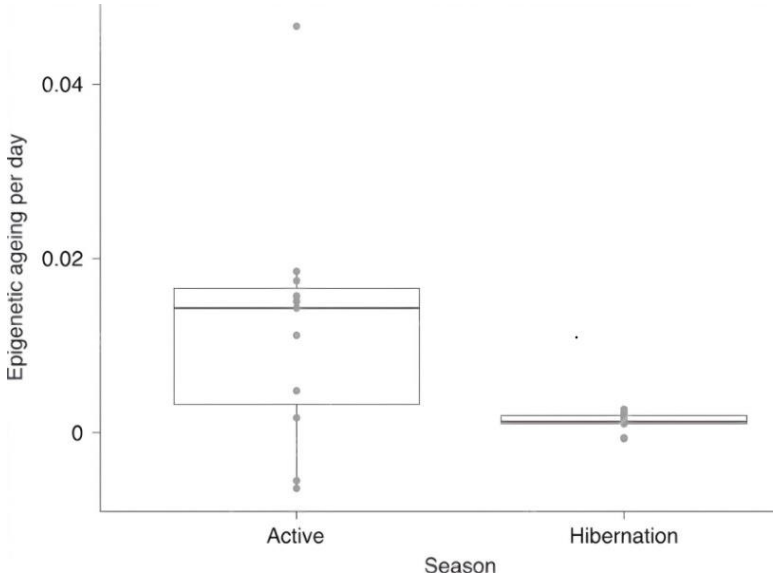

Figure 2. Epigenetic aging rates of 11 yellow-bellied marmots calculated from the EPM model. Negative aging rates and the highest aging rate in the active season were all old females (Source: Pinho et al. 2022).

Human life expectancy has drastically increased in the past century alone. In the United States, for example, the average lifespan has risen from an expected 47.3 years in 1900 to 78.9 years by 2010 due to vast improvements in living conditions and medical care, as illustrated in Figure 2 (Crimmins 2015). Moreover, some factions of the scientific community argue that human lifespan could be indefinitely extended with the right technology, while other groups have placed a ceiling at 115 years but acknowledge that the cap could increase if enough advancements are made to slow aging on numerous fronts, which seems impossible with current technology (Keshavan 2018). Considering the implications on longevity that torpor has for other animals, it's possible that torpor is the next piece of technology in the endless struggle to bring death to a pause.

Effects on Diseases

It is hypothesized that, because hibernation slows down cell metabolism and growth, it could be used to that effect on cancer cells, slowing tumor growth. An experiment conducted in 1954 by Lyman and Fawcett monitored tumor growth of sarcoma implanted in the cheeks of hamsters, comparing growth during hibernation to a non-hibernating control group in normal temperatures as well as 5°C. They found that the cool temperatures of the 5°C non-hibernating group stunted tumor growth marginally, but hibernation had the most significant impact on the tumor, essentially stalling its growth until arousal where the tumor returned to a normal growth rate (Lyman and Fawcett 1954). This study is old and comes prior to the shift towards modern peer-review that begin in the 1970s, so its results may not be as reliable as modern studies (Baldwin

2019). Considering cancer is positively correlated with higher basal metabolic rates due to oxidative stress, it is reasonable to infer that a metabolic depression state such as torpor could help reduce cancer risk (Dang 2012). Induced hypothermia has reduced mutative effects of radiation, suggesting that torpor states could also be used to improve and reduce risks of current cancer treatments (Baird et al. 2011).

In addition to cancer treatment, torpor may be able to treat or prevent numerous other ailments, including metabolic diseases like obesity and type II diabetes. Hibernators show an increased intrinsic control over their endocrine system, which allows them to enter an obese, insulin-resistant state going into hibernation and just as easily exit these states once they finish hibernating (Wu et al. 2013). Manipulation of hibernation-related genes could similarly allow for conditional control over obesity and type II diabetes in humans as well (Wu et al. 2013). Hibernators also have reduced risk for muscular atrophy, osteoporosis, and myocardial atrophy, due to a significant increase in RNA-binding protein motif 3 and atrial stiffness during hibernation (Berg von Linde et al. 2015). This suggests that hibernation genes could be used as a therapeutic treatment for similar diseases, including heart failure (Berg von Linde et al. 2015).

Possible Consequences

There is concern that hibernation treatments could lead to a stalled immune system in patients. Since the immune system is an immense energy consumer and operates most often by inducing fever, an increase in core body temperature, studies have shown that it may be entirely or almost entirely shut off during torpor, meaning a period of arousal is required for the animal to resume immune response and fight off pathogens (Canale and Henry 2011). It appears that a natural failsafe exists, considering when hibernating mice were injected with e. coli cells to stimulate an immune response during torpor, the result was a reduced torpid state and increased minimum core temperature during torpor, and some were prevented from entering a torpid state at all (Canale and Henry 2011). This suggests that a sterile environment is pertinent to patients eligible for torpor treatment, and that torpor would not be a valid treatment for patients exhibiting pathogenic illnesses.

Furthermore, questions regarding cost, integrity, and consent should be addressed. The implication that temperature reduction may be necessary to enter and maintain torpor suggests that a sterile, temperature-controlled room would be necessary. The average cost for ICU treatment a decade ago was $4,300 per day (Halpbern 2019). Even without inflation factored in, that number reduces the pool of eligible patients to wealthier individuals, unless insurance adds torpor to the list of covered treatments. Additionally, if the patient in indefinite torpor treatment is accused of committing a felony, when should they be awakened for the investigation, if at all (Bloomberg Quicktake contributors 2022)? These, among many other uncertainties regarding safety and liability require answers before torpor treatments could make their way to the mainstream, assuming synthetic induction methods succeed in human trials.

DISCUSSION

After centuries of fascination in human hibernation, it may finally come to scientific fruition (The Encyclopedia of Science Fiction contributors 2016). The sheer number of advancements in recent years suggest that torpor may become available as a medical treatment within this lifetime, and media exposure keeps interest and funding alive (Bloomberg Quicktake contributors 2022). If Anna Bågenholm and John Smith could survive extended periods underwater due to apparent metabolic rate depression, then purposefully applying such a technique in a controlled environment opens the opportunity for many medical applications that are otherwise out of reach (MacDonald 2014, Ortiz 2015). Researchers have identified temperature control as a necessary component of synthetic torpor induction and H_2S as an essential torpor regulator (Cerri 2016, Kabil, Vitvitsky and Banerjee 2014). The next step is pairing effective chemical inducers, possibly 5'-AMP, with controlled environmental temperature reduction to find ways to safely maintain a longer torpor state, and moving the most viable to larger animal trials, such as primates, before testing on humans (Wu et al. 2007). With the potential benefits of increased lifespan and treatments to a variety of diseases, the ethical uncertainties related to torpor pale in comparison to its applications, and many of these concerns may well diminish once human trials are underway.

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