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REVIEW | *Synthesis*

Shallow metabolic depression and human spaceflight: a feasible first step

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Regan MD, Flynn-Evans EE, Griko YV, Kilduff TS, Rittenberger JC, Ruskin KJ, Buck CL. Shallow metabolic depression and human spaceflight: a feasible first step. *J Appl Physiol* 128: 637–647, 2020. First published January 30, 2020; doi:10.1152/japplphysiol.00725.2019.—Synthetic torpor is an induced state of deep metabolic depression (MD) in an organism that does not naturally employ regulated and reversible MD. If applied to spaceflight crewmembers, this metabolic state may theoretically mitigate numerous biological and logistical challenges of human spaceflight. These benefits have been the focus of numerous recent articles where, invariably, they are discussed in the context of hypothetical deep MD states in which the metabolism of crewmembers is profoundly depressed relative to basal rates. However, inducing these deep MD states in humans, particularly humans aboard spacecraft, is currently impossible. Here, we discuss shallow MD as a feasible first step toward synthetic torpor during spaceflight and summarize perspectives following a recent NASA-hosted workshop. We discuss methods to safely induce shallow MD (e.g., sleep and slow wave enhancement via acoustic and photoperiod stimulation; moderate sedation via dexmedetomidine), which we define as an ~20% depression of metabolic rate relative to basal levels. We also discuss different modes of shallow MD application (e.g., habitual versus targeted, whereby shallow MD is induced routinely throughout a mission or only under certain circumstances, respectively) and different spaceflight scenarios that would benefit from its use. Finally, we propose a multistep development plan toward the application of synthetic torpor to human spaceflight, highlighting shallow MD's role. As space agencies develop missions to send humans further into space than ever before, shallow MD has the potential to confer health benefits for crewmembers, reduce demands on spacecraft capacities, and serve as a testbed for deeper MD technologies.

anesthesia; hibernation; sedation; sleep; spaceflight; torpor

INTRODUCTION

When faced with an energetic challenge such as food shortage or hypoxia, some animals employ metabolic depression (MD), a regulated and reversible reduction in metabolic rate below basal metabolic rate (47, 106). MD reduces the requirements for food and O_2, thereby extending survival in energetically challenging times and environments. The scope of MD spans orders of magnitude, ranging from basal metabolic rate to ametabolism (i.e., a lack of detectable metabolic rate), and the taxonomically diverse set of animals that employ MD such as the hibernators and daily heterotherms do so to varying degrees along this continuum (106; Fig. 1).

While humans are not capable of naturally expressing profound MD, artificial induction of MD (i.e., synthetic torpor) could provide benefits to a variety of biomedical treatments and long-duration human spaceflight (13, 24, 26, 36, 75, 92, 96, 110). With respect to the latter application, theoretical benefits to spaceflight fall into two categories: logistical and biological. Logistically, synthetic torpor could reduce rates of crewmember consumables use (food, water, O_2) and CO_2 production as torpor does in animals that naturally express this metabolic state. Collectively, MD would reduce demands placed on spacecraft mass, volume, and power capacities, which, due to the constraints these capacities place on launch

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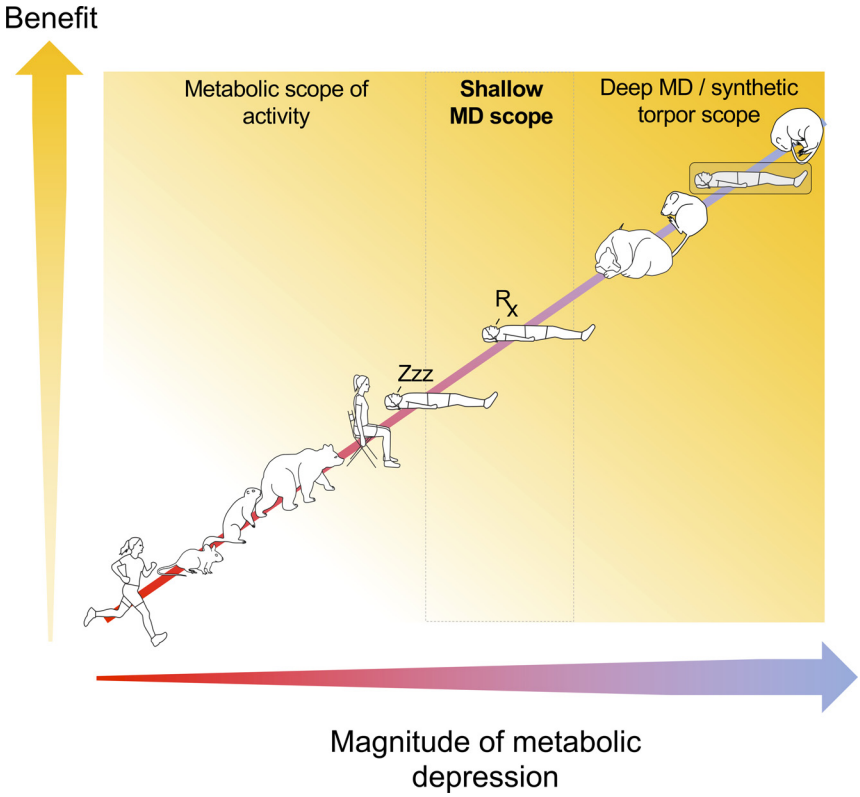

Fig. 1. A qualitative depiction of how the magnitude of metabolic depression (MD) imparts theoretical benefits to human spaceflight, with "benefit" comprising positive effects on crewmember health, reduced demands on the spacecraft, and reduced mission cost. As the magnitude of MD increases (i.e., as metabolic rate is depressed; represented by red-to-blue transition of the line), benefit increases (represented by white-to-gold transition of the background). Images plotted on the line represent different metabolic rate states grouped into the three categories titled atop the figure. From *left* to *right*, these include: humans while active; mouse (daily heterotherm), arctic ground squirrel (hibernator), and black bear (hibernator) while active; human while resting; human while sleeping; human while under sedation or anesthesia; and bear, mouse, human, and ground squirrel while in states of torpor (naturally induced for bear, mouse, and ground squirrel; synthetic torpor for human). Deep MD/synthetic torpor states would confer the greatest benefits, but they currently cannot be induced in humans. Shallow MD states, such as those during slow wave sleep and sedation, currently can be induced in humans and may be used in targeted or habitual ways aboard spacecraft. Shallow MD has the potential to benefit the health of crewmembers, reduce demands on the spacecraft and thus mission cost, and serve as a testbed for future deeper MD technologies.

limits, could make long-duration human spaceflight more cost-effective and thus feasible. Biologically, synthetic torpor could enhance crewmembers' resistance to radiation and micro/zero-gravity-induced and -associated negative health outcomes as is seen in animals that naturally express torpor (8, 9, 40, 49, 55, 57, 58, 76, 83, 89, 90, 112, 125). For example, mammals in natural hibernation exhibit dramatically enhanced survival rates when they are irradiated to a similar intensity as is seen in space compared with conspecifics in the active state (8, 90). Hibernating mammals also exhibit remarkably low rates of bone and muscle atrophy following 6 to 8 mo of physical inactivity associated with hibernation (40, 49, 55, 58, 83, 125). Finally, the hibernation state in mammals is characterized by profound reduction in metabolic rate and in some cases a switch in metabolic fuel use from mixed fuel to lipid metabolism (17, 101), both of which confer advantages to long-duration spaceflight. Although specific mechanisms of hibernation are not fully resolved, current work seeks to elucidate and understand if mechanisms underlying the hibernation phenotype are inherent to torpor per se and therefore potentially inherent to synthetic torpor as well (116). In addition to mitigating the deleterious effects of radiation, disuse atrophy, and energetic demands and concomitant waste production, synthetic torpor would effectively remove crewmembers from the challenging psychosocial environment of a cramped, isolated, and cohabitated spacecraft. Taken together, these attributes suggest synthetic torpor has the potential to simultaneously mitigate the five major hazards of long-duration human spaceflight specified by NASA's Human Research Program, and, generally speaking, the deeper the state of MD, the greater the benefits. These benefits have been the focus of numerous recent articles as space agencies and private companies develop programs to return humans to deep space and contemplate going further than ever before.

Recently, NASA hosted a workshop (https://www.nasa.gov/sites/default/files/atoms/files/ocswebsite_spacetorporworkshop.pdf) at Ames Research Center (Moffett Field, CA) to explore the potential of synthetic torpor during short- and long-duration human spaceflight. Attendees included a group of ~50 experts from diverse fields, including human and veterinary medicine, spaceflight, and hibernation biology. The group sought to determine how MD or some form of synthetic torpor could help advance spaceflight capability and identify the knowledge gaps required to advance synthetic torpor for spaceflight application. Despite the theoretical benefits of deep synthetic torpor states to spaceflight and recent promising advances (6, 12, 16, 25, 33, 45, 61, 62, 72, 79, 95, 104, 116, 121), it was generally agreed that the scientific understanding necessary to safely and reversibly induce deep MD states in humans, a challenge compounded by limitations associated with being aboard a spacecraft, is currently too rudimentary to realistically help NASA attain its more immediate goals. By contrast, shallower states of MD could be more feasibly induced and would confer numerous benefits.

The recent articles on application of synthetic torpor to spaceflight scenarios have focused exclusively on deep synthetic torpor states. This article is the first to explore the application of relatively shallow states of MD to spaceflight. We define shallow MD as a state in which metabolic rate is reduced only ~20% below basal levels compared with the 80–98% reductions typical of hibernators. In addition to its conferred benefits and greater feasibility, shallow MD could also complement other ground-based and on-orbit experiments in the development of deeper MD states. Below, we discuss

some spaceflight scenarios that would benefit from shallow MD and then describe some natural and artificial methods (e.g., sleep, sedation) by which such states could be induced. We end by outlining a possible sequence of experiments toward further developing this technology and highlight the role shallow MD might play in this development.

SPACEFLIGHT SCENARIOS THAT WOULD BENEFIT FROM SHALLOW METABOLIC DEPRESSION

There are two ways in which shallow MD could be used to benefit a variety of spaceflight scenarios: targeted and habitual. The targeted use of shallow MD involves inducing this metabolic state only under specific circumstances. Targeted induction, for example, could be employed during emergency situations, specifically those that threaten crewmember health due to either the depletion of consumables or the toxic accumulation of CO_2 in the spacecraft. Crewmembers aboard the International Space Station (ISS) are exposed to partial pressures of CO_2 (P_{CO_2}) of ~4 mmHg. For comparison, atmospheric P_{CO_2} is ~0.3 mmHg. Levels >5 mmHg promote fatigue, sleep disorders, and impaired concentration (73). Thus, a malfunctioning CO_2 scrubber could rapidly result in CO_2 levels that would compromise crewmember health and performance and, by extension, the mission. Shallow MD could be employed to decrease CO_2 production and thus extend the life of the CO_2 scrubber and consequently the time available for repairs or rescue. Shallow MD would also slow the rate of consumable use, thus extending their availability. The extent to which MD reduces consumables use would depend on the duration and depth of MD, and the savings enabled by shallow MD would theoretically and by definition be less than those enabled by deep MD states. Nevertheless, considering the 7–8% decrease in metabolic rate for every 1°C decrease in core body temperature (T_b), a relatively small 2°C reduction in core T_b could reduce rates of CO_2 production and consumable use by up to 16% (84).

An emergency scenario that might have benefited from shallow MD occurred during Shuttle mission STS-107 in 2003. The wing damage that caused *Columbia* to disintegrate upon reentry was known to NASA within 24 h of launch (19), and plans for a crew rescue operation (as well as a repair operation) were evaluated (20). The rescue involved preparing another Shuttle, *Atlantis*, for launch so as to rendezvous with *Columbia* in orbit, allowing the suited STS-107 crew to transfer from *Columbia* to *Atlantis* via ropes. The orphaned *Columbia* would then be de-orbited by mission control and ditched in the Pacific Ocean. This plan, deemed "challenging but feasible," required *Atlantis*'s processing to outpace consumables use by the STS-107 crew. The flight surgeons calculated that the limiting consumable would be the cabin CO_2 scrubbers, and NASA predicted that, if the crew's consumables were rationed and the processing and launch of *Atlantis* proceeded as planned, there would be a 5-day window for rescue before *Columbia*'s consumables ran out (20). Ultimately, it was decided based on modeling outcomes that the wing damage would not jeopardize reentry, so the rescue mission was abandoned. The point here is to highlight a realistic scenario that would benefit from shallow MD. Reducing the crew's rates of consumables use and CO_2 production via shallow MD would have proportionately extended the opportunity time for success had the rescue mission been pursued.

The habitual use of shallow MD involves inducing this metabolic state routinely over the course of longer-duration missions, such as to Mars. For example, habitual induction could take the form of extended sleep durations. One of the lessons learned from the ISS is that crewmembers sleep ~6 h daily despite being allotted 8 h for sleep (7). In humans, the endogenously generated circadian day is typically longer than 24 h (30, 39). Normally, light exposure on Earth entrains (synchronizes) the human circadian rhythm to geophysical time, resulting in the 24-h rest/activity cycle. The ISS orbits the Earth every 90 min, far faster than the human circadian rhythm can accommodate; thus, crewmember circadian cycles become misaligned internally and extrinsically (42). In addition, light exposure before awakening is associated with poor sleep quality (93). Sleep deficiency increases energy expenditure (63); results in the accumulation of sleep debt, which negatively impacts psychological status and optimal productivity (100); affects neuronal and glial signaling pathways (51) in ways that lead to slower reaction time, impulsivity, and decreased overall performance (22, 37); and may ultimately lead to cardiovascular disease (70, 86). These effects will likely be exacerbated during long-duration missions to deep space (i.e., beyond low Earth orbit). Calculations predict that the total travel time for a Mars mission using current propulsion technology and a Hohmann transfer orbit will be ~18 mo (71), during which crewmembers will be in an enclosed space and in constant close proximity. Furthermore, radio transmissions will take up to 22 min to reach Earth (2-way light time up to 44 min), limiting the ability of mission control to arbitrate disputes and solve problems. Extending and improving sleep could both alleviate psychosocial pressures that lead to disputes and enhance crewmember performance, especially during emergency situations. Aside from the health benefits of sleep, prolonged sleep would also reduce rates of consumable use and CO_2 production, resulting in a reduced consumable requirement and/or an enhanced reserve pool of various consumables should the mission be prolonged. Based on measurements of energy use during different sleep and wake states (63), extending sleep duration to 8 h from the current ISS average of 6 h would reduce each crewmember's overall energy use by 3.4% during a hypothetical Mars mission with 540 days travel time. This reduction of this magnitude predicts similar reductions in mass and volume requirements for each crewmember.

Both targeted and habitual use of shallow MD hold the promise of clear benefits to spaceflight scenarios, but how might such states be induced or controlled?

SHALLOW STATES OF METABOLIC DEPRESSION IN HUMANS

Although humans are usually not considered a species that is inherently capable of MD, shallow MD states can be induced in humans both naturally and artificially. Below, we explore sleep as a natural state of MD and anesthesia (specifically, sedation) as an induced state of MD.

Natural metabolic depression in crewmembers through sleep. Sleep is a systemic condition in which the eyes are closed, postural muscles are relaxed, and responsiveness is decreased. Sleep comprises three non-rapid-eye movement

(NREM) stages and one REM stage that are distinguished by measurement of electroencephalographic (EEG) activity of the brain, electromyographic (EMG) activity of the skeletal musculature, and electrooculographic (EOG) activity that indicates eye movements. All states of sleep and wakefulness exhibit a range of frequencies in the EEG, but some states have predominant frequency characteristics. For example, low-amplitude alpha waves (8–12 Hz) predominate in the EEG during relaxed wakefulness with the eyes closed. NREM stage 1 (N1) is a shallow sleep state generally occurring at the transition between wakefulness and sleep and in which alpha and theta waves (4–7 Hz) occur. N2 is a deeper sleep state typified by theta activity and sleep spindles (bursts of oscillatory neural activity between 11 and 16 Hz usually lasting ~0.5 s). N3 is a deep sleep state typified by high-amplitude low-frequency delta waves (0.5–4 Hz) and is hence referred to as slow wave sleep (SWS). Finally, REM sleep is a state in which the skeletal muscles exhibit low muscle tone as measured in the EMG, rapid eye movements are detected in the EOG, and the EEG displays low-amplitude high-frequency alpha and theta activity similar to wakefulness, but the sleeper is more difficult to awaken (69). Cerebral blood flow and metabolic rates are higher during REM sleep than in other sleep stages and equivalent to those during wakefulness (80, 102). Of the four sleep stages, metabolic rate reaches a nadir during N3 (SWS); cerebral metabolic rate is reduced by ~25% (80), which, when combined with the energetic savings that arise from the fasting and reduced physical activity of sleep, depress whole body metabolic rate by 20–25% relative to typical waking rates (43). In fact, both hibernators and daily heterotherms enter torpor via SWS, leading to the hypothesis that torpor is an evolutionary extension of SWS (10, 52, 64, 110).

The mechanisms involved in shallow MD during sleep appear to be sleep stage dependent. During N3 SWS, brain O_2 consumption, glucose metabolism, and insulin secretion are reduced, producing an overall reduction in systemic glucose utilization (14). Because of the reduced metabolism associated with decreased muscle tone during inactivity, glucose levels remain stable throughout N3 relative to inactive wake (54). Chronic sleep deprivation increases blood glucose concentrations, impairs glucose tolerance, and reduces sensitivity to insulin, further supporting the role of sleep in reducing energy consumption (97, 114).

Sleep and energy metabolism are closely linked through shared neural centers (118). For example, the hypocretin/orexin (Hcrt) neurons of the lateral hypothalamus regulate energy metabolism by sensing peripheral energy signals such as glucose, insulin, and amino acids and respond by promoting feeding or increased energy expenditure so as to maintain energy homeostasis (54, 67). From a sleep perspective, the Hcrt system is involved in controlling arousal via the receptors Ox1R and Ox2R (63). This system also interacts with hormones that are altered by sleep. For example, the satiety hormone leptin is produced by adipocytes during sleep (111) while the appetite-stimulating hormone ghrelin is suppressed during sleep (113). Both hormones interact with the Hcrt system in ways that help maintain energy metabolism; for example, leptin inhibits the Hcrt neurons and their wake-promoting effects, whereas ghrelin stimulates them.

Another neural cell group involved in sleep and energy metabolism is the melanin concentrating hormone (MCH) neurons, which are coextensive with the Hcrt neurons in the lateral hypothalamus (11). From an energy metabolism perspective, MCH neurons promote positive energy balance, since both MCH peptide deletion and targeted MCH neuron ablation result in lean, hyperactive, and hypermetabolic mice (3, 65, 109, 120, 123). Because extracellular glucose activates MCH neurons (18) and functional expression of ATP-sensitive potassium channels is necessary for glucose sensing by these cells (66), MCH neurons appear to play a role in regulating glucose homeostasis and insulin sensitivity. MCH neurons are also involved in regulation of REM sleep (59, 119, 120), and ablation of these cells results in a partial insomnia (117).

The cell types above are under finely tuned control via the excitatory neurotransmitter glutamate and the inhibitory transmitter γ-aminobutyric acid (GABA). The firing rate of Hcrt neurons, for example, is highest during active wakefulness and lowest during NREM and REM sleep. The source of GABAergic inputs that inactivate these cells during sleep is uncertain, but there is evidence for inputs from the preoptic area (2), zona incerta (77), and local GABA cells (41). Conversely, the firing rate of MCH neurons is highest during REM sleep and lowest during active wakefulness (50); presumably, local GABA release suppresses the activity of these cells during wakefulness.

In addition to sleep per se, circadian rhythms contribute to the shallow MD observed during sleep. The circadian pacemaker is located in the suprachiasmatic nucleus of the hypothalamus, where it coordinates many aspects of biological function, including synchronizing the sleep-wake cycle with the 24-h solar light-dark cycle (31) and rhythmic production of hormones such as melatonin and cortisol. Some of the circadian processes that intersect with hibernation, torpor, and sleep include thermoregulation and metabolomic signaling. The daily rhythm of core body temperature is under central circadian control, with a nadir occurring during the inactive phase, while peripheral skin temperature displays the inverse pattern (68). Similarly, the daily fluctuation in concentration of circulating fatty acids is under circadian control, with levels peaking around noon among entrained individuals, while many amino acids show circadian variation at different circadian phases (32). Leptin also shows a circadian modulation independent of the behavioral sleep-wake cycle, with a peak during the biological night (111). Glucose and insulin exhibit a circadian rhythm when measured under constant conditions over 24 h (87, 108) that is typically masked by the postprandial glucose response to meals. The postprandial glucose response exhibits circadian variation in postprandial glucose response, with better glucose tolerance in the biological morning compared with the biological evening (88).

The shallow metabolic depression induced by sleep could be harnessed to benefit human spaceflight. Spaceflight crewmembers typically achieve only 6 h of sleep per night while in low Earth orbit (7), and they spend ~20% of their time in a misaligned circadian state (42). Crewmembers frequently report using hypnotics (7), such as zaleplon and zolpidem (35), that increase sleep duration in terrestrial patients with insomnia. In space, the use of hypnotics reduces sleep latency but does not increase sleep duration or quality (7). It is unclear how hypnotics alter sleep architecture during spaceflight, but recent ground-based studies suggest that using rhythmic acoustic stimulation can enhance slow waves during NREM sleep (91). Enhancing SWS through acoustic stimulation appears to in-

crease parasympathetic activity (48) and may reduce overall glucose utilization. However, this hypothesis remains untested. Alternatively, SWS may be enhanced pharmacologically. For example, γ-hydroxybutyrate (GHB), a naturally occurring neurotransmitter that functions as a $GABA_B$ receptor agonist (81), can be administered orally as sodium oxybate. Although GHB is typically used in the treatment of cataplexy and narcolepsy, it also induces slow wave activity. However, the use of GHB as a SWS enhancer will require additional research.

Another approach to maximizing the benefits of shallow MD for spaceflight would be to increase total sleep time to terrestrial norms of 7–8 h/night. Such a modest sleep extension could not only reduce life support system requirements for long-duration missions but may also allow for a reduced payload due to decreased caloric needs. At present, it is not possible to dampen or eliminate the circadian arousal system; however, strategies that maintain circadian entrainment to the imposed sleep-wake schedule may be effective. Careful control of light and darkness can prevent circadian misalignment, which is associated with shorter sleep duration in space (42). In addition, control of light and darkness may allow for entrainment to a "short-day" photoperiod. In a ground-based study, strict adherence to a short-day photoperiod with 10 h of light and 14 h of darkness lengthened sleep duration to an average of 11 h/night (122). Similarly, a recent study demonstrated that a natural short-day photoperiod lengthened sleep duration to nearly 10 h/night (115). Although manipulating sleep through maintenance of a short-day photoperiod may have some benefits, short-day photoperiods may contribute to seasonal affective disorder in the subset of individuals who are prone to depression and sensitive to short photoperiod (124). Further study is required to determine whether the risks and benefits are acceptable when considering the use of short photoperiods in isolated and confined environments.

Induced metabolic depression in crewmembers through anesthesia or sedation. Anesthesia is a controlled state in which sensation and/or awareness is temporarily lost (82). Typically used in medical settings, anesthesia allows procedures to be performed that would otherwise be too technically complex and/or painful for the patient. There are four levels of sedation by anesthesia: minimal sedation, an anxiolytic state in which the patient's cognition and coordination are impaired, but they respond normally to verbal cues; conscious sedation, a deeper state in which the patient responds purposefully to verbal or tactile stimuli; deep sedation, in which the patient responds to repeated verbal or tactile stimuli and respiration may be impaired; and general anesthesia, in which the patient is unresponsive, and intervention may be required to maintain respiratory and cardiovascular function (97a). A transition from sedation to anesthesia can sometimes be achieved by increasing the administered dosage of a single agent (e.g., propofol). Some drugs produce only sedation and may provide analgesia but not general anesthesia (e.g., dexmedetomidine). An additional added benefit to sedation is that it may reduce body temperature by 1–2°C (107) and thus reduce MR.

Most anesthetic agents, including potent volatile (i.e., inhaled) anesthetics such as isoflurane and intravenous agents such as propofol, are hypothesized to act on GABA receptors (44). One current hypothesis of general anesthesia is that these drugs act through subcortical centers involved in the control of sleep-wake states. Several studies have identified GABA receptors on neurons in the ventrolateral preoptic and median preoptic nuclei that are active during REM and NREM sleep (53). General anesthetics may also inhibit wakefulness-promoting centers, such as the anterior hypothalamus, and appear to inhibit connectivity between different regions of the brain, inhibiting the processing of information (82). For example, propofol produces EEG changes that are remarkable for highly structured rhythmic activity (98). These changes include paradoxical excitation, strong frontal alpha oscillations, and burst suppression. Ketamine and dexmedetomidine appear to act on the same neuronal circuits in the brain as propofol but target *N*-methyl-D-aspartate (NMDA) and α_2-adrenergic receptors, respectively. Ketamine is an anesthetic agent that antagonizes NMDA receptors and, among other effects, appears to promote a SWS pattern by decreasing cholinergic activity in the pons (38). It is commonly described as a dissociative anesthetic, and its effects are mediated by blockade of excitatory synaptic activity (53). NMDA receptors found on inhibitory neurons appear to be less sensitive to the effects of ketamine than those on excitatory neurons. Ketamine is therefore thought to preferentially inhibit excitatory-to-excitatory coupling more than inhibitory-to-excitatory coupling, thus producing analgesia and hypnosis (4). Dexmedetomidine is an α_2-adrenergic receptor agonist that is commonly used as a sedative in the intensive care unit and operating room. Activation of α_2-adrenergic receptors causes membrane hyperpolarization and decreases calcium conductance, both of which depress neuronal firing. The locus coeruleus is the predominant noradrenergic nucleus in the brain and modulates vigilance and referral of nociceptive signals. It has the highest density of α_2-receptors in the central nervous system and is thought to be responsible for the sedative and analgesic effects of dexmedetomidine (29, 85).

Anesthetic agents are typically chosen by clinicians based on the preoperative health of the patient and the goals of the procedure. These goals may include analgesia, neuromuscular blockade, unconsciousness, and blunting of the stress response, and they may be achieved by administering different combinations of agents so as to optimize surgical conditions while minimizing risk to the patient. General anesthesia typically requires substantial infrastructure and continuous monitoring of the patient. Volatile anesthetics require an anesthesia gas machine to vaporize and deliver the drug and O_2 at set rates while removing CO_2, whereas intravenous drugs such as propofol require an infusion pump to do so. The patient's breathing may require support with mechanical ventilation, and monitors must include electrocardiography, blood pressure, O_2 saturation, respiratory gas monitoring, and body temperature. The shallower state of anesthesia induced by conscious or moderate sedation also requires physiological monitoring but does not require airway management or mechanical ventilation (28).

Moderate sedation may be the ideal anesthetic state for inducing shallow MD aboard spacecraft. It would reduce metabolic demands of crewmembers while minimizing biological risks and the necessary life support infrastructure, such as mechanical ventilators. Protocols using intravenous dexmedetomidine have been successful in suppressing shivering and permitting MD for up to 6 h (21, 103). Moreover, dexmedetomidine does not impair performance on the psychomotor vigilance test (1) and, in fact, has been shown to significantly reduce postoperative cognitive dysfunction in rodent models

and elderly patients (27, 34, 60, 74, 78, 99). Conversely, general anesthesia commonly leads to impaired cognitive performance in patients in the days to weeks following anesthesia, regardless of whether the patients were awake or comatose upon being anesthetized (94). For side effects that occur during sedation (e.g., bradycardia), these can be mitigated by pharmacological intervention or stimulating the crewmember (103), which would require at least one crewmember to remain in an active normal metabolic state so as to monitor vital signs and titrate medications if needed.

Achieving shallow MD states aboard spacecraft through moderate sedation will require noninvasive induction methods, especially if the state is to be induced habitually. The habitual use of shallow MD via moderate sedation may occur during sleeping hours. For example, at the beginning of an 8-h sleep time, a crewmember could apply a transdermal patch and then self-administer an intranasal medication. The intranasal dose would have a rapid effect while the transdermal patch would administer medication more consistently over the course of the sleep time. If a short-acting α_2-adrenergic agonist such as dexmedetomidine were used, the patch could release medication gradually over only the first 6 h and then allow the drug to be metabolized for the final 2 h so as to minimize sedation side effects upon waking (56). Coordinating the administration with the circadian rhythm ("chronotherapy") may optimize the agent's effects or even result in synergistic effects (23, 105). Crewmembers could be monitored using noninvasive respiratory and cardiac monitors, permitting early detection of any vital sign changes and the opportunity for other crewmembers or an automated system to manage the sedated crewmember and address the abnormality. Overall, this method of inducing shallow MD through moderate sedation could be applied habitually as described, or in a targeted fashion under specific circumstances. In either case, it has the potential to reduce rates of consumables use. For example, assuming a 2°C reduction in T_b (107) and an 8% decrease in metabolic rate for every 1°C reduction in T_b (84), 6 h of moderate sedation per day would reduce each crewmember's total energy expenditure by ~4%; 8 h would equate to a 5.4% reduction. The rates at which crewmembers used consumables and produced CO_2 would be reduced proportionately, allowing for mass and volume savings and/or a larger reserve of consumables.

PERSPECTIVES AND PATHS FORWARD

The theoretical benefits of applied MD states (i.e., synthetic torpor) to human spaceflight have generated much discussion. However, the biological and logistical challenges of inducing deep MD states in spaceflight crewmembers are significant and will require substantial resource investment to support experimentation and innovation. There is currently little evidence to suggest that human physiology could support the safe and reversible induction of deep states of MD and low T_b akin to mammalian hibernation. For example, reductions in T_b below 28°C are known to cause a host of physiological problems in humans such as pulmonary edema and refractory cardiac arrhythmias (5). Even if these deep MD states could be induced in spaceflight crewmembers, the necessary infrastructure to support them would require entirely new spacecraft designs (15) and likely exceed the mass, volume, and power savings conferred by deep MD.

To seriously pursue this technology, a development plan involving a sequence of ground-based and on-orbit experiments should be developed and executed to quantify the cost-benefit relationship of using torpor during spaceflight scenarios. This will provide empirical evidence to what is currently a theoretical idea and, thus, help justify what will likely be a large resource investment. Below, we present a multistep development plan toward applying synthetic torpor to human spaceflight, including the use of shallow MD.

Step 1. Develop a safe, reversible, and reliable method for inducing synthetic torpor in homeothermic endotherms, such as rats, and eventually, humans. Rapid advancements toward this are currently being made, and they involve elucidating the natural mechanisms by which mammals, such as hibernators, induce torpid states and using this information to develop methods of inducing similar metabolic states in nonhuman mammals that do not naturally induce MD. Generally, this development is being done in the context of biomedicine, where synthetic torpor (or analogous "suspended animation" states) may facilitate organ preservation and transplant, as well as the treatment of ischemia-reperfusion injury associated with stroke and heart attack. Synthetic torpor technology will likely be developed for such biomedical scenarios, not human spaceflight. The upshot is that spaceflight agencies/companies may be able to harness this development for spaceflight application, meaning their upfront resource investments may be minimal. However, because the method(s) for inducing synthetic torpor states will be developed to work in a laboratory or hospital setting, their eventual application to spaceflight will likely require considerable modification, and this may be expensive (elaborated on below).

Step 2. Once *step 1* is achieved for rats (humans will take longer), a series of ground-based experiments should be run to gather evidence on synthetic torpor's value to spaceflight before embarking on a series of more expensive and challenging on-orbit experiments. The ground-based experiments could be run in parallel to continuing efforts toward safely inducing synthetic torpor in humans and should involve the following: *1*) determine whether synthetic torpor states confer the same protection against ionizing radiation that natural MD states are known to. These experiments should be performed on homeothermic endotherms in states of synthetic torpor and could be carried out at NASA's Space Radiation Laboratory at Brookhaven National Laboratory to best mimic space-type radiation; and *2*) determine whether animals in synthetic torpor use fewer consumable resources (food, water, O_2, CO_2 scrubbers) than conspecifics in a normal metabolic state.

Step 3. If the results of *step 2* suggest synthetic torpor will benefit spaceflight, then a series of on-orbit experiments should be run. The goals here will be to determine whether natural torpor can be safely, reversibly, and reliably induced in space and to verify whether it confers biological and logistical benefits to spaceflight. These experiments could be as follows: *1*) on-orbit experiments using natural MD animals (e.g., hibernators) to confirm that they can enter and maintain MD in space and, if so, whether the MD expressed in space does indeed reduce rates of consumables use. This will confirm that natural MD can be safely and reversibly induced in space and that MD does reduce consumables use; both are currently presumptions. These experiments could be conducted aboard the ISS whose large capacities for consumables storage relative

to those of, say, an autonomous spacecraft would enable the use of a small mammalian hibernator such as the meadow jumping mouse (*Zapus hudsonius*); *2*) on-orbit experiments using natural MD animals to confirm that MD use does indeed mitigate the damaging effects of continuous micro/zero-gravity and radiation exposure. This experiment would need to take place outside Earth's Van Allen Belts to ensure the correct radiation environment, which would preclude its execution aboard the ISS. Rather, it would likely take place aboard an autonomous spacecraft in cis-lunar orbit. Its samples would need to be recovered to enable proper analysis, which would require atmospheric reentry. The ideal model organism for this experiment would be sufficiently small to fit aboard the spacecraft in appropriate numbers, yet sufficiently large and complex to be relevant to the application of synthetic torpor to humans in space and to enable the appropriate postflight analyses. One possibility is land snails (e.g., *Otala lactea*), which reliably induce MD in low-humidity environments, are large enough to enable various tissue-level analyses, have successfully flown in space before, and that have survived the rigors of ballistic reentry; *3*) the development of a reliable, noninvasive protocol to induce shallow MD in humans for 8 h. This would permit measurement of metabolic, cognitive, and/or physical changes resulting from shallow MD along with their duration effects. It is probable that sex, baseline fitness, and body anthropomorphics will affect drug metabolism and the manifestation of shallow MD in humans. These nuances should be characterized before shallow MD is used in the austere environment of space; and *4*) shallow MD use by astronauts aboard the ISS as a first step toward confirming the benefits of MD use by humans. As well as providing this preliminary evidence to support the pursuit of deeper MD technologies, this use of shallow MD by crewmembers would also impart the benefits described earlier in this manuscript.

Step 4. If the results of *steps 1*, *2*, and *3* suggest synthetic torpor can be safely induced in humans and will benefit spaceflight, then resources could be allocated toward adapting the infrastructure required to induce these metabolic states to the restrictive spacecraft environment. This will involve: *1*) minimizing the infrastructure required to achieve synthetic torpor so as to fit aboard a spacecraft; *2*) minimizing the steps involved in inducing, sustaining, and recovering from synthetic torpor, as well as monitoring a torpid crewmember's condition, so as to be feasibly used by a spaceflight crew aboard an isolated spacecraft; *3*) minimizing recovery time to ensure torpid crewmembers can be responsive and useful in the case of an emergency; and *4*) developing a cycle of synthetic torpor use by crewmembers to ensure at least one crewmember is in an active metabolic state at all times so as to operate the spacecraft, communicate with mission control, and monitor torpid crewmembers' conditions. Ideally, this cycle will avoid circadian misalignment.

While we have placed shallow MD in *step 3* because of its function as a feasible first step toward exploring MD use by humans in space, it is important to note that shallow MD serves more uses than this and should be pursued in parallel with the other steps and for its own purposes. Further research into its spaceflight-related use is required. Some ground-based next steps may include experiments investigating: photoperiod-related sleep entrainment; SWS enhancement via acoustic stimulation; SWS induction via dexmedetomidine administration; the potential for shallow MD states to protect against ionizing radiation (46); and the effects of induced sleep and/or shallow MD on motor and cognitive performance. The latter is particularly important when considering the ability of a crewmember to self-rescue in the event of an emergency. As NASA, other space agencies, and private entities develop missions to send humans further into space than ever before, shallow MD, whether targeted or habitual, has the potential to confer health benefits for crewmembers, reduce demands on spacecraft capacities, and serve as a testbed for future deeper MD technologies.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

M.D.R., E.E.F.-E., Y.V.G., T.K., J.C.R., K.J.R., and C.L.B. conceived and designed research; M.D.R. prepared figures; M.D.R., E.E.F.-E., Y.V.G., T.K., J.C.R., K.J.R., and C.L.B. drafted manuscript; M.D.R., E.E.F.-E., Y.V.G., T.K., J.C.R., K.J.R., and C.L.B. edited and revised manuscript; M.D.R., E.E.F.-E., Y.V.G., T.K., J.C.R., K.J.R., and C.L.B. approved final version of manuscript.

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