Be cool to be far: Exploiting hibernation for space exploration

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Abstract: In mammals, torpor/hibernation is a state that is characterized by an active reduction in metabolic rate followed by a progressive decrease in body temperature. Torpor was successfully mimicked in non-hibernators by inhibiting the activity of neurons within the brainstem region of the Raphe Pallidus, or by activating the adenosine A1 receptors in the brain. This state, called synthetic torpor, may be exploited for many medical applications, and for space exploration, providing many benefits for biological adaptation to the space environment, among which an enhanced protection from cosmic rays. As regards the use of synthetic torpor in space, to fully evaluate the degree of physiological advantage provided by this state, it is strongly advisable to move from Earth-based experiments to 'in the field' tests, possibly on board the International Space Station.

Keywords: Torpor, Hibernation, Synthetic Torpor, Space Exploration, Radioprotection.

INTRODUCTION

Torpor is a peculiar biological condition that, in mammals such as squirrels, hamsters, mice, bears, bats, and others, is characterized by an active reduction in metabolic rate that causes a progressive decrease in body temperature, proportionally to the thermal gradient between the body and the ambient (Heldmaier et al., 2004). The state of torpor can be considered as the basic building brick of a more complex behavior, such as hibernation. The term torpor usually refers to a single bout of metabolic suppression lasting from a few hours to a few days. Hibernation is a sequence of torpor bouts, often interrupted by brief interbout arousals, lasting around 24 hours (Geiser, 2020, 2013).

The decrease in body temperature in these hypometabolic states can either be extreme, such as in the arctic ground squirrel, one of the mammals able to reach a below-zero temperature (Barnes, 1989; Ruf and Geiser, 2015), or mild, such as in the grizzly bear, the temperature of which rarely drops below 30°C (Nelson and Robbins, 2015). However, even animals living at high ambient temperatures are able to enter torpor (Grimpo et al., 2013; Nowack et al., 2020).

The basic aim of torpor/hibernation is to induce a reduction in metabolic rate that allows hibernators to survive for a long period in adverse environmental conditions, with no access to food or water, but little is known about the mechanism controlling this state. Seasonal hibernators, such as the arctic ground squirrel, have a strong drive to enter hibernation before the arrival of winter. The body of these animals pre-adapts to the hibernation season, reducing, for instance, testicular volume or thyroid activity (Jastroch et al., 2016). These changes suggest that a genetic regulation of this behavior is at work (Schwartz and Andrews, 2013). Other mammals, such as the Siberian hamster, display daily episodes of torpor that are well entrained with their circadian rhythm (Cubuk et al., 2016), whereas other mammals, the so-called facultative heterotherms (such as the mouse), enter torpor only if their energy balance becomes negative (Oelkrug et al., 2011).

Despite the multiple phenotypes and regulations of the appearance of hibernation/torpor, it is reasonable to think that there is a single underlying mechanism that reduces metabolic rate. This could potentially be used by other conditions that induce a reduction in metabolic rate, such as the diving reflex, non-rapid eye movement (NREM) sleep (Silvani et al., 2018), or states in which thermoregulatory control appears to be impaired, such as rapid eye movement (REM) sleep (Capitani et al., 2005; Cerri et al., 2017). The mechanism whereby this occurs is not known at the moment, but some preliminary observations point in the direction of the hypothalamus, and in particular the Dorsomedial Hypothalamus (DMH)(Hitrec et al., 2019) and to a newly discovered set of neurons within the Preoptic area (Hrvatin et al., 2020; Takahashi et al., 2020). A complete understanding of the molecular mechanism triggering torpor would be of great help in the quest to develop a procedure to induce this state in humans (Cerri, 2017a).

At the moment, three procedures have been shown to be effective in mimicking a state that very much resembles torpor in non-hibernators: 1) the inhibition of the neurons located within Raphe Pallidus (RPa), a region located in the brainstem (Cerri et al., 2013); 2) the activation of the adenosine A1 receptor in the brain (Tupone et al., 2013); 3) a cocktail of drugs, including xenon, delivered in liposomes (Zakharova et al., 2021, 2019); the activation of the hypothalamic Q neurons (Takahashi et al., 2020) All these methods require more translational research before being used for space exploration, but the objective to be pursued is now clear, and this ambitious goal is no longer out of reach.

It is important to highlight that the degree of resemblance to the most significant torpor features by each of these procedures may vary. Hypothermia by itself differs from torpor, since it requires the overwhelming of the physiological defense by cold: external cooling may even induce an increase in metabolic rate, the opposite of what a technology aimed at mimicking torpor tries to achieve (Nakamura and Morrison, 2008). All of these procedures though don't rely on physical cooling, but, on the contrary, act by inhibiting, in different ways, the central drive for

thermogenesis, favoring the induction of a reversible, undefended, centrally-induced hypothermia. The results is that the dynamics of adaptation of many physiological variables to this hypothermic/hypometabolic condition may still differ from what it is described for natural torpor (Geiser et al., 2014; Swoap et al., 2007; Vicent et al., 2017), while many others have been shown to go in the same direction, such as, for instance, the slowing of the rhythms of the electroencephalogram (EEG) (Cerri et al., 2013; Tupone et al., 2013), the after-bout rebound of slow wave sleep (Cerri et al., 2013), the reversible phosphorylation of the Tau protein (TP) (Luppi et al., 2019), the increase in cell radioresistance (Tinganelli et al., 2019).

Something more specific needs to be said about two key features of torpor: i) the maintenance of some degree of thermoregulation once a new temperature balance is reached; ii) the ability of the animals to arouse spontaneously from the hypometabolic/hypothermic state. It was shown that thermoregulation can still be activated in hibernators even during the bout of hypothermia (Florant and Heller, 1977; Heller and Colliver, 1974; Ortmann and Heldmaier, 2000), a feature that was so far mimicked only by the activation of Q neurons in mice (Takahashi et al., 2020). Although this important feature shows that torpor is a highly regulated behavior, in a translational view and in an artificial environment, thermal balance during synthetic torpor could be achieved by regulating the ambient temperature. This is especially important in the view that if thermoregulation was somehow still active, it could lead to an increase in energy consumption that may not be optimal for a long permanence in hypometabolism. The maintenance of an optimal energy balance is also critical in view of the periodic arousals that characterize seasonal hibernators, since, during the arousal, energy usage goes way up together with the production or reactive-oxygen species (ROS). The ability to spontaneously arise from hypometabolic states is also crucial since it separates torpor from other "knock out" conditions. So far, a spontaneous arousal was described for all the four procedures for synthetic torpor listed before. A technology that could harvest the advantage of torpor may therefore lead to something different from natural torpor, in a similar fashion to what happened in the field of aeronautics, where aircrafs were developed by obeying to the general physics of flight, and not by strictly trying to replicate the mechanism of wings-flapping typical of birds.

Many of the changes encountered by the body during hibernation could in fact be extremely helpful for humans in a long-term space exploration mission (Choukèr et al., 2019; Nordeen and Martin, 2019). Among the most interesting features we can highlight: the reduced food and water requirement, reduced waste production, reduced awareness, preservation of muscle strength and bone structure, slowed aging, and enhanced radioprotection against radiation damage. The reduced need for supplies, such as food and water, is a direct consequence of the reduced metabolic rate, that is also the cause for the reduced production of biological waste.

Another interesting feature of torpor is radioprotection. Passive shielding and reduction of exposure duration are currently the predominant approaches to protect astronauts, putting substantial constraints on space mission designers. Studies on the resistance of hibernators to very high levels of X- and γ-rays a few decades ago showed that hibernation drastically enhances radioprotection; however, there is still a lack of experimental data as to whether the protective effects measured in X- and γ-rays could be extended to the spectrum of ionizing radiation encountered in space. While extensive experiments have not yet been performed, current technical capabilities would allow for the experimental assessment of torpor and hibernation in counteracting the effects of exposure to ionizing radiation and micro-gravity in space.

Unfortunately, micro-gravity research in animal models offers few analogues. Neither hindlimb suspension protocol nor parabolic flight studies would be appropriate to study the long-term effects of microgravity on hibernators, but the International Space Station would be the ideal place to conduct such studies. We hope that a future research program on torpor/hibernation may use this essential facility, accelerating the development of a very promising technology.

PHYSIOLOGICAL ADAPTATION DURING HIBERNATION

Terminology

Hibernation-like state, torpor-like state, hypometabolism, hypothermia, deep hypothermia, suspended animation, stasis, and probably others are some of the terms that are used in the field of translating hibernation to humans. Recently, the expression synthetic torpor was suggested (Cerri, 2017a), and also used by NASA and others (Griko and Regan, 2018; Regan et al., 2020). In this paper, we will use the expression synthetic torpor to refer to a hypometabolic state that is induced by artificial means in either hibernators or non-hibernators, and that resembles, at least partially, the state of natural torpor.

Physiological adaptation in hypometabolic states

During both natural hypometabolic states such as torpor/hibernation, and artificial ones, like synthetic torpor, many organs and systems show major changes in response, or in adaptation, to the new body condition. Many of these adaptations may be exploited for health purposes as well as in vision of long-term human space flights.

The brain

The brain is among the organs showing the most drastic changes during torpor. In squirrels, synaptic spines were shown to be largely reabsorbed in many portions of the cerebral cortex, and also of the hypothalamus (Von Der Ohe et al., 2007, 2006). The reduction in the number of synapses may be an adaptive response aimed at reducing the high energy expenditure of the brain. Synapses are in fact among the highest consuming portions of neurons. With such a drastic reduction in synapses, the overall computational capability of the brain is likely to be reduced. It is reasonable that this drop in cortical connectivity will prevent the brain from sustaining complex cognitive tasks, partially or totally, reducing the degree of awareness or consciousness (Cerri, 2017b). Synapses are then reformed very quickly after the return to normothermia (Von Der Ohe et al., 2007, 2006). At the moment, little is known regarding the characteristic of the reformed synapses compared with the re-absorbed ones: are they in the same location? Do they have the same strength? This very peculiar event could be an interesting model with which to study synaptic plasticity (Peretti et al., 2015), but it should also be considered with caution in the case of a long space trip in a hypometabolic state. The time needed for the rewiring of the brain must be taken into account, in the event of emergency arousal, since enough time has to be allowed for the recovery of full cognitive capacity. It is also unclear at the moment whether the neural rewiring could be compromised by other factors, such as drugs or sleep (Zamboni et al., 2004; Baracchi et al., 2008), or the presence of specific genes.

Beside the reduction in the number of synapses, during a torpor bout neurons also present changes in some of their key cellular functions. In particular, TP becomes hyperphosphorylated, both in hibernators (Arendt and Bullmann, 2013) and in non-hibernators (Chiocchetti et al., 2021; Hitrec et al., 2021; Luppi et al., 2019). This molecular change resembles the one key change suggested to be at the origin of neurodegeneration in Alzheimer's Disease (Arendt et al., 2015). Data from non-hibernators suggest that the hyperphosphorylation of the TP (P-TP) may be temperature-dependent (Guisle et al., 2020), but other hypotheses are possible. For instance, starvation also promotes P-TP, that could therefore be linked to a reduced metabolism more than to hypothermia (Planel et al., 2001; Yanagisawa et al., 1999). The effect of hypothermia may be only secondary to the metabolic suppression induced by the decrease in temperature, but the specific role of hypothermia vs. hypometabolism in the status of the TP has yet to be elucidated. The purpose of P-TP increase is not known at the moment. Does it serve to protect some structure of neuronal cytoskeleton from damage? Or does it promote a further reduction in energy consumption by lowering the axonal transport (Wang and Mandelkow, 2016)? In terms of mechanism, the accumulation of P-TP is apparently mediated by a relative increase in kinase activity compared to phosphatase activity (Planel et al., 2007, 2004; Su et al., 2008). What is clear is that, shortly after the arousal, P-TP is cleared from the brain. It is certainly suggestive that, in torpor and in synthetic torpor, the brain can be seen as 'diving' into a quickly reversible dementia.

In terms of brain function, an interesting question regards the characterization of torpor and synthetic torpor as reflected in the electroencephalogram (EEG). Is it something akin to sleep? Or to coma? Or to general anesthesia? EEG is strongly affected by temperature, since conduction velocity decreases according to the Q10 factor, leading to a left-shift of the EEG spectrum (Deboer, 1998). However, the reduced number of synapses observed in torpor may also produce effects. EEG recordings during torpor show a signal of low amplitude and low frequencies, differing from all the known sleep stages (Vyazovskiy et al., 2017). EEG recordings in synthetic torpor show a similar pattern, with frequency bands, like the Theta band, shifting to lower frequencies with the lowering of the brain temperature, mirroring something that could be called "slow wakefulness" (Cerri et al., 2013). Apparently, sleep does not appear during torpor, with the possible exception of REM sleep, signs of which were reported to occur in torpid lemurs (Blanco et al., 2016). The absence of sleep, or at least of its EEG signs, during torpor suggests that torpor may be a period of sleep deprivation (Deboer and Tobler, 2003; Royo et al., 2019). Indeed, a long bout of intense sleep rich in slow waves, can be observed in hamsters and in squirrels after the arousal from torpor/hibernation (Deboer and Tobler, 2000; Larkin and Heller, 1999; Strijkstra and Daan, 1998), as well as in lemur (Royo et al., 2019), and in rats after synthetic torpor (Cerri et al., 2013). The nature of this sleep, however, is still controversial. Depriving hamsters of the after-torpor sleep induced a further sleep-rebound, proportional to the length of the torpor bout (Deboer and Tobler, 2003), but the same was not observed in squirrels (Strijkstra and Daan, 1998). More recently, some differences in the nature of the slow wave during recovery sleep as compared to after-torpor sleep have also been reported (Vyazovskiy et al., 2017). Differences in body temperature (much lower in squirrels than in hamsters), or duration of the torpor bout (weeks for squirrels, hours for hamsters) may justify the difference. In mice, no increase in slow waves was reported during sleep soon after torpor, but the short duration of these bouts may be insufficient to induce a sleep debt (Lo Martire et al., 2020). Moreover, the degree of energy expenditure for body rewarming to recover a body temperature of 37°C may also influence sleep intensity after the torpor bout (Cerri et al., 2013). The role of the after-torpor sleep is a factor to be carefully evaluated in the hypothesis of torpor use for space travel. It is possible that the sleep rebound may be an essential part of the "re-synaptization" of the brain, or of the clearance of the P-TP. Are there consequences if such sleep is prevented? Or does it have to be protected and considered as part of the arousal process? All these questions will have to be addressed before considering the use of synthetic torpor for space exploration.

The gastrointestinal tract

The gastrointestinal tract (GI) is affected by hibernation in a variety of ways. As a matter of fact, the GI tract is a combined organ, merging the actual digestive system and the microbiota living in it. These compartments are affected both by temperature and fasting, the latter being especially prolonged during seasonal hibernation.

In general, the changes in the physiology of the GI tract during hibernation are in tune with the general melody of metabolic suppression: the cell cycle stops together with all digestive processes. Mucosal size and protein content, as well as villus height, were shown to be reduced during hibernation (Carey, 1990), but a complete atrophy of the mucosa cannot be afforded by the animal, since the GI tract has to be ready to absorb nutrients shortly after arousal. It is probably for this reason that, when the stimulating effect of food presence is lacking, an enhanced area-specific absorption of sodium and glucose takes place on the mucosa. (Carey, 1990; Weitten et al., 2016). Interestingly, the barrier becomes generally leakier, since the number of gap junctions decreases (Carey et al., 2012). Under normal circumstances, this could be a problem, exposing the organism to infection from the residential microbes, but during hibernation an increase in the lymphocytes occurs in the GI tract, possibly preventing microbial invasion (Bouma et al., 2010a; Kurtz and Carey, 2007).

The microbiota is also significantly changed by hibernation, and the lack of nutrients, coupled with the decrease in body temperature, reshapes the bacterial population in the GI tract (Carey and Assadi-Porter, 2017): taxa feeding on host-derived substrates (such as muciniphilia) tend to prevail over taxa requiring diet-related substrates, such as Lachnospiracea (Carey et al., 2013; Dill-McFarland et al., 2014; Stevenson et al., 2014). Changes in microbiota

were also shown to induce changes in metabolism when transplanted (Sommer et al., 2016), possibly playing a role in guiding or favoring the metabolic suppression in hibernation.

Multiple aspects of GI tract adaptation to hibernation could be useful in the medical field (Sisa et al., 2017), but some aspects will require special consideration in vision of a use in space. Atrophy of the GI tract will have to be prevented at all costs, and so far there is no indication as to how the GI tract adapts to long periods of synthetic torpor. It is possible that some strategy will have to be envisioned to maintain GI absorption functionally ready to be activated after the arousal. The composition of the microbiota also has to be kept in consideration, by designing specific probiotics to help the transition from a low-metabolism microbiota to a high-metabolism one.

The immune system

The activity of the immune system during torpor/hibernation presents some interesting changes, the main one being the drastic reduction in circulating white cells (Bouma et al., 2010a). Leukopenia has been reported in multiple species (Bouma et al., 2013, 2011, 2010b; Frerichs et al., 1994; Huber et al., 2021; Reitsema et al., 2021; Reznik et al., 1975; Spurrierl and Dawe1, 1973; Suomalainen and Rosokivi, 1973; Tøien et al., 2001; Webb et al., 1982), affecting all types of immune cells (granulocytes, lymphocytes, and monocytes). This drastic drop in the number of white cells poses multiple questions: 1) do the white cells die? Or 2) is the production of white cells halted? And 3) does this immunosuppression make animals more susceptible to infections?

As far as the first two questions are concerned, at the moment the data suggest that the white cells do not go into apoptosis or die for other reasons, but are mostly segregated in reservoir organs, such as the liver, the spleen, the lymph nodes, or the walls of blood vessels (Bouma et al., 2011; Inkovaara and Suomalainen, 1973; Yasuma et al., 1997), justifying the fast onset of leukopenia as well as the rapid return of white cells to the bloodstream after arousal (Bouma et al., 2011; Suomalainen and Rosokivi, 1973). The segregation of white cells is also coupled with a reduced production rate of new white cells, probably the consequence of the general decrease in the cell cycle (Szilagyi and Senturia, 1972).

The third question opens a more complex scenario. As a matter of fact, hibernators do not die from infectious diseases during hibernations, with the most relevant exception of the recent epidemic of White Nose Syndrome (WSN) in bats. WSN is caused by a fungus that seems to be able to grow comfortably at the temperature usually reached by bats during hibernation, with devastating consequences for the bats (Foley et al., 2011). Interestingly, bats mostly die from depletion of energy reserves because animals must warm up more often to fight against the fungi which causes the diseases, rather than from the infection itself. Interestingly, European bats seem to be able to organize a more effective immune response against the fungus, balancing the increased energy request of the immune system with the opposite metabolic needs. Apart from the WSN, it does not seem that hibernators are more susceptible to other kinds of infective disease during hibernation. A possible explanation is that, in sensitive organs, such as the lungs or the intestine, an increase in the number of white cells was reported (Inkovaara and Suomalainen, 1973), suggesting that some sort of immune barrier is attending these sensitive body regions. Interestingly, an activation of neuroinflammation has also been reported for the Syrian hamster (Cogut et al., 2018). Furthermore, the consequences of this transient immunosuppression could also spread to the period immediately after arousal, if the white cell count is not quickly normalized (Havenstein et al., 2016).

Beside the white cell count, the overall immune response is blunted during hibernation (Bouma et al., 2013; Jaroslow and Serrell, 1972; Prendergast et al., 2002); it is not clear, at the moment, if this is an effect mediated by temperature or if it is something that happens specifically during torpor/hibernation. Hypothermia has been shown to reduce the immune response also in non-hibernators (Ding et al., 2018; Jiang et al., 2013), but no data regarding inflammation during synthetic torpor are currently available.

In the case of any hibernation-derived technology to be used in long-term space travel, the degree of immunosuppression would have to be carefully assessed for a potential use in space, limiting the crews's susceptibility to developing possible infective diseases.

Locomotor system

The mass of skeletal muscle is the result of the balance between protein synthesis and protein degradation that is physiologically correlated with the mechanical loading on the muscle (Miyazaki and Esser, 2009). Disuse atrophy of the skeletal muscle is the consequence of the reduced protein synthesis and this, in turn, is consequential to the reduced mechanical load in conditions such as prolonged bed rest (Bodine, 2013). Permanence in microgravity is another condition in which the reduced mechanical load on the locomotor system leads to muscle atrophy and bone demineralization (Demontis et al., 2017). At the moment, there are no effective countermeasures that can prevent this condition, and even the daily routine of physical exercise that astronauts are required to follow on board the ISS is not sufficient to preserve the function of the locomotor system (Hargens et al., 2013).

During hibernation, seasonal hibernators are often subject to extended periods of muscle inactivity and fasting, but do not experience disuse atrophy (Bertile et al., 2021; Cotton, 2016; Giroud et al., 2010; Ivakine and Cohn, 2014). Interestingly, the functionality of the skeletal muscle of the locomotor system is preserved both in small hibernators such as the squirrel, that are able to reach a very low body temperature (Andres-Mateos et al., 2012), and in larger hibernators such as the bear, whose body temperature does not drop below 30°C (Harlow et al., 2001). If the hibernator's skeletal muscle were to lose strength, the survival of the animal would be compromised at the moment of arousal.

The mechanism allowing hibernators to preserve the majority of their muscle strength is not fully known (Tessier and Storey, 2016). In the brown bear, an increase in anabolic intracellular signaling may counteract the rest-stimulated catabolism; moreover, the muscle fibers switch to a slow oxidative phenotype and potentiate mitochondrial biogenesis (Miyazaki et al., 2019), changes that are similar to those observed in squirrels (Xu et al., 2013). Although more research is necessary to fully elucidate the degree of preservation of muscle strength and the underlying molecular mechanism, the preservation of the lean mass that have been observed in these may offer a great improvement of the quality of life of astronauts facing a long permanence in space, once the underlying mechanism will be exploitable.

Bones of astronauts are also subject to a demineralization that requires a longer time on Earth to be compensated for (LeBlanc et al., 2007). Demineralization seems to be non-homogenous through the body segments, occurring to a greater degree in the portions that are more subjected to weight load. Similar to skeletal muscle, multiple reports show that bone structure of hibernators is maintained during hibernation (Doherty et al., 2012; McGee-Lawrence et al., 2011; Utz et al., 2009; Wojda et al., 2016, 2012). Larger hibernators seem to achieve this goal through different and more effective mechanisms than smaller hibernators, since the former do not experience any bone loss (McGee-Lawrence et al., 2008). The molecular mechanisms preventing bone loss in hibernators are not fully known, and the role of the central nervous system may be marginal (Cravens et al., 2020) The endocrine system may play a major role, coordinating calcium metabolism and metabolic request (Doherty et al., 2014; McGee-Lawrence et al., 2008), but specific molecular changes in the metabolism of fatty acid and in the endocannabinoid system in bones during hibernation have been reported (Doherty et al., 2016, 2012).

The integrity of the locomotor system is critical for the human exploration of the solar system. Astronauts will have to be able to spend a long time in microgravity and then be able to operate when reaching the surface of other planets. At the moment, the only countermeasures that are considered are compensatory physical exercise and exposure to artificial gravity. A biological countermeasure to the microgravity-induced muscle atrophy and bone demineralization will extend the ability of humans for space exploration and will also have relevant medical applications; hibernation seems to hold the optimal biological counter measurement to this problem.

Response to radiation damage

Cosmic radiation represents an important threat to the health of astronauts during long space flights, and, so far, the only strategy to counteract this threat is the use of passive shielding, a solution that does not provide full

protection from the damage, thus limiting the ability of humans to participate in long-term space exploration (Durante and Cucinotta, 2008). A biological strategy aimed at protecting living tissues from radiation damage can therefore produce a relevant improvement, extending humans' possible time of permanence in space (Baird et al., 2011).

In light of the biological relevance of such a feature, the resistance to radiation damage found in hibernators was intensively studied a few decades ago (Kuskin et al., 1959; Musacchia and Barr, 1968; Prewitt and Musacchia, 1975). Briefly, most of the studies investigated the effects of lethal X or Gamma irradiation on hibernators and showed that hibernators increase their probability of survival for each dose tested during the hibernation period, even though later studies pointed out that the radiation damage may remain silent during hibernation, and express itself after awakening (Sazykina and Kryshev, 2011). This last observation, together with the lack of methods to induce hibernation in non-hibernators, and the lack of a biological explanation of the enhanced (or at least transient) radioresistance, seemed to indicate that hibernation was not a valuable way of improving radioprotection for long-term space flights.

Recently, new data and hypotheses have stirred renewed interest in the topic (Petit et al., 2018). Beside the methods shown to induce a torpor-like state in non-hibernators (Cerri et al., 2013; Tupone et al., 2013; Zakharova et al., 2019), new promising molecular substrates that play a valuable role in cell protection have been identified; these include the family of proteins called "Cold Shock Protein" (CSP) (Lleonart, 2010; Peretti et al., 2015) and the Cystathionine β synthase/Hydrogen sulfidepathway, activated by monoamines such as serotonin and dopamine (Dugbartey et al., 2015; Giroud et al., 2021). Moreover, the reduction in oxygen metabolism during hibernation may well provide additional protection against radiation damage. As far as this latter point is concerned, it is important to notice that differences in the dynamics of awakening may affect the overall health status of the animal (Cerri et al., 2013). Moreover, the studies conducted on Earth on radioresistance in hibernators have so far used X-rays or γ -ray irradiation. No study has yet investigated the radioresistance of hibernators to the charged particle component of cosmic rays, which plays a major role in radiation exposure in interplanetary space (Durante, 2014).

Cosmic rays are composed of a mixture of particles of galactic and solar origin, with high-energy charged particles representing the prevalent component in open space. Galactic cosmic rays and particles emitted by the sun during so-called Solar Particle Events (SPEs) present several issues as far as radiation protection is concerned. For instance, it has been estimated that intense SPEs might expose unshielded astronauts to life-threatening doses of radiation (Kim et al., 2009). In fact, due to the high energy of these particles, it is extremely difficult to set up efficient spacecraft shielding with the current technologies, mainly because of the heavy passive materials that are required. Specifically, protons in the energy range 102-105 MeV give the largest contribution in terms of fluence (about 85%). Heavier ions are also present in a much lower percentage (about 15%), but they contribute to an equivalent dose to that of protons, in view of their enhanced quality factor (Durante and Cucinotta, 2011). Moreover, interaction of cosmic rays with the shielding itself leads to further modifications of the radiation spectra to which astronauts are eventually exposed. Concerning long-term interplanetary travel it might thus be useful to quantify the eventual dose-sparing factor that could be associated with induced torpor (Tommasino and Durante, 2015).

Overall, the understanding of the physiology of hibernation could be very useful to make human exploration of the solar system possible (Cerri et al., 2016; Puspitasari et al., 2021), but could also be exploited to improve the treatment or outcome of numerous clinical conditions (Cerri, 2017a) that are treated with radiation.

Aging

Aging is a very relevant issue for space exploration. Recent data from NASA suggest that the exposure to space radiation may have curious effects on telomere length (Welsh et al., 2019), raising the issue of how space can affect aging. Because of their connection with metabolic rate, telomeres has been well studied in hibernators (Nowack et al., 2019). Telomeres were shown increase their length during torpor bouts (Turbill et al., 2012), suggesting that the aging process may be slowed down. However, in two species of dormice, telomere's length was shown to

decrease during interbout arousal, possible because of the increased oxidative stress resulting from the increase in mitochondrial respiration (Giroud et al., 2014; Hoelzl et al., 2016a; Turbill et al., 2013). The degree of metabolic activity of tissues plays in fact a role in the dynamics of telomere changes in length (Wilbur et al., 2019). However, and quite surprisingly, adult edible dormice can re-elongate their telomeres during the summer season (Hoelzl et al., 2016b; Turbill et al., 2013), even if this could be a feature specific , although interesting, of the species (Hoelzl et al., 2016b).

How the length of telomeres and the speed of the molecular aging process can impact future space travel is still unknown. For instance, the role of arousals from synthetic torpor has to be carefully assessed, since they could dampen the advantages of torpor by increasing the level of oxidative stress. The research on telomeredynamics opens two key questions for the application in humans. The first one is about at what body temperature humans should be maintained in synthetic torpor. Would a bear-like form of synthetic torpor be more effective than a squirrel-like one? The second question is about the arousals: what are they for? And are they indispensable? The degree of oxidative stress the body will be subjected to during the arousal may be a critical variable to be taken into account to design a correct plane of synthetic torpor, that could maximize the advantages of metabolic suppression, minimizing potential tissue damage.

TOWARD HUMAN HIBERNATION

Evolution

The evolution of hibernation supports the idea that humans could be able to enter such a state. This very peculiar trait is an ancestral trait, probably present in the proto-mammal, and the proto-mammal is proposed by many to be a heterotherm (Lovegrove, 2017). Protomammals appeared about 150-200 million years ago, carrying with them some interesting new traits. The transition from reptiles to mammals forced the organism of the latter to orchestrate a more complex array of physiological regulation to exploit the considerable advantages of the higher metabolic rate that characterizes mammals. Compared to reptiles, the metabolic rate of mammals is about 7- to 10-fold higher; much of this energy usage is devoted to homeothermy, the ability to maintain the temperature of the body independent from the temperature of the environment. Protomammals were nocturnal animals, probably to avoid predation from the smallest dinosaurs, such as the velociraptor, the miniraptor, or the microraptor, and were able to maintain an optimal working temperature for muscles and the brain, thanks to their higher metabolism. Such high energy usage must have required a continuous search for food during the phase of activity but may also have become sustainable thanks to a drastic reduction in metabolic rate aimed at saving energy during the resting phase. After the extinction of most of the dinosaurs, the risk of predation was very much reduced, providing an advantage for these species, that were able to reproduce rapidly and expand in other ecological niches.

Indeed, from the presence of metabolic suppression in the phenotype of the proto-mammals, it can be argued that the gene set needed for surviving such a phenotype may be common among modern mammals. The species that are able to activate some kind of metabolic suppression are indeed non-clustered or confined to a specific order (Melvin and Andrews, 2009), as it would be if torpor was a more recent development. This suggests that humans may also possess such a genomic inheritance, a hypothesis strengthened by the discovery of a hibernating primate (Dausmann et al., 2004).

Cases and history

For a long time the induction of human torpor or human hibernation has been considered some sort of science fiction wishful thinking and a target outside our reach, to be confined to movies and novels (Lee, 2008). It would no doubt be considered one of the greatest discoveries of science, but, looking carefully at medical records, it is

very interesting to see that human torpor may have already happened in the history of our species. In this regard, we can divide the medical records into three categories: i) cases reported to have survived extreme cold; ii) cases in which deep hypothermia was induced in a medical setting; iii), and cases resembling torpor under many aspects. It is important to stretch out the differences between these three categories, since the beneficial effects of hypothermia in terms of survival do not necessarily uses the same mechanisms of cellular protection of torpor. Nevertheless, patients surviving deep accidental hypothermia or induced into deep hypothermia in hospitals may help hibernation research in understanding the role played by hypothermia during torpor.

Cases reported to have survived extreme cold

Today, it is not difficult to find records or reports of people surviving for many hours with no heartbeat in circumstances in which they were exposed to severe cold. From the 17th century is the case of Anne Greene: a lady sentenced to death by hanging in London (Breathnach and Moynihan, 2009), to the much more recent case of of Anna Bågenholm , maybe the most famous case of its kind (Gilbert et al., 2000).

Cases of deep hypothermia induced in medical settings

In the years between 1938 and 1940, Dr. Tample Fay also experimented with deep hypothermia (Fay, 1959). Dr. Fay is known as "the man who broke the cold barrier" (Alzaga et al., 2006), since he was the first to truly venture into the realm of deep hypothermia, as an innovative treatment for cancer As a result, Dr. Fay suggested that if hypothermia had some protective effect toward cancer, it may also have some therapeutic effects (Wang et al., 2006). Patients affected with multi-metastatic cancer were therefore induced into a deep hypothermia, in a later case even down to 9°C (Niazi and Lewis, 1958). Although the treatment did not cure cancer, all the patients recovered from the treatment with no side effects. Even if the treatment did not work, Dr. Fay's intuition may have been on the right track: later studies showed that cancer seems to halt its progress during hibernation (Lyman and Fawcett, 1954).

Cases resembling torpor

An earlier interesting report comes from the British Medical Journal of 1900 ("Human hibernation," 2000). In an anonymous short article with the evocative title "human hibernation", the story of the small Russian town of Pskov is told. Apparently, during winter, the inhabitants' of this town gathered together in a large construction in the center of the town where they would "go to sleep" in small cells and sleep the winter off, waking up again in spring. As far as we know, there is no other confirmation of this story, but it is worth mentioning. Another possible case of torpor in humans can be found in a short piece from Oliver Sacks:the story of Uncle Toby (Sacks, 2019). Uncle Toby was a patient who, apparently, remain for 7 years in a state of stasis, fed and taken care of by his family, as a consequence of a severe form of hypothyroidism.

An immunological cause was suggested as an explanation for a case reported in 2002 in the journal Neurology (Magnifico et al., 2002). This patient complained of excessive fatigue after a self-reported flu or flu-like syndrome. A 5-day recording of his body temperature showed recurring episodes of morning hypothermia at around 6:00 am, that was in no way different from the daily torpor episode that can be observed in animals such as the hamster during the winter season. It is still unclear what caused such episodes since no clear sign of brain or organ dysfunctions was found.

Another observation that supports the hypothesis that humans could enter torpor/hibernation is found in the measurements of metabolic rate in human fetuses (Singer, 2004, 1999; Singer and Mühlfeld, 2007). The fetus' metabolism, adjusted for body mass, places it on a different body size-metabolism curve compared to other

mammals, with a greater resemblance to hibernating mammals. Fetuses are exposed to the high body temperature of the mother and to a lower oxygen tension than adults, conditions that could both influence metabolic rate.

In conclusion, although rare, medical reports are supportive of the possibility that humans could enter torpor/hibernation.

INDUCING SYNTHETIC TORPOR

Synthetic torpor could be induced in multiple ways (Dirkes et al., 2015), and drastically differs from hypothermia-induced lethargic hypothermia (Popovic, 1960). From recent works (Cerri et al., 2013; Tupone et al., 2013), the most promising approach seems to be the inactivation of the central pathways controlling thermogenesis. These pathways and their relationship with thermoregulation have been examined in detail (Morrison and Nakamura, 2019). In theory, every area in the network could be the target for the induction of Synthetic Torpor.

Exploiting the central thermoregulatory pathway

To defend their body temperature, mammals monitor ambient temperature and body temperature (see Figure 1 for a schematic drawing of the brain network for temperature regulation). The sensing of the external temperature is located mostly in the skin (Filingeri, 2016). Other districts, such as the respiratory mucosae (Cruz and Togias, 2008), or the oral cavity (Lemon, 2017), may be able to detect temperature, but their role has not yet been extensively studied. From the skin, two separate sensorial pathways arise: one for cold sensing (Nakamura and Morrison, 2008), and the other for warm sensing (Nakamura and Morrison, 2010). Most of the receptors involved in temperature sensing are part of the Transient Receptor Potential (TRP) channel family (Wang and Siemens, 2015). TRPM8, for instance, is an important cold receptor, activated by the natural agonist menthol (Babes et al., 2010); TRPV1, on the other hand, is an important warm receptor, activated by the natural agonist capsaicin (Szolcsányi, 2015). Both warm and cold information is relayed in the Parabrachial Nucleus (PBN), located in the brainstem, in two distinct portions of the nucleus itself. Cold afferences are relayed in the External Lateral PBN whereas warm afferences are relayed in the Dorsal Lateral PBN (Madden and Morrison, 2019). Although it seems critical, the role of skin temperature information in modulating the central control of body temperature is still under discussion (Romanovsky, 2014), since is not clear how environmental temperature is computed in the central thermoregulatory areas (Berner and Heller, 1998).

The brain has another temperature sensitive area located in the Preoptic Area (POA) (Conti, 2018). The receptors responsible for such sensing are not fully known (Siemens and Kamm, 2018), but the existence of warm sensitive neurons and cold sensitive neurons have been proven multiple times (Alam et al., 1995; Parmeggiani et al., 1987). The classic view on the dynamics of temperature control was based on the idea of a set point, probably inspired by the early work of Norbert Wiener of Cybernetics (Wiener, 1948). The brain was thought to read its own temperature, compare it with a temperature of reference, and activate the necessary line of defense: heat production or heat dissipation. This view was challenged, and a more recent interpretation of the general mechanism for the preservation of body temperature is based on the idea of open-loop, in which every thermal effector acts independently from the others, based on different thresholds of activation (Romanovsky, 2007). In this latter case, body temperature would not be encoded in the brain, but would be the result of the independent activation of multiple circuits controlling each single effector. Therefore, thermal information is transmitted from the peripheral temperature sensing nerves and reaches the POA, which is considered the master thermoregulatory area. From here, a descending output is thought to reach the DMH and, from here the key relay area of the RPa.

DMH neurons are involved in multiple aspects of thermoregulation, mediating the preoptic-to-raphe connection controlling cold defense (DiMicco and Zaretsky, 2007), but are probably also involved in the control of torpor

(Hitrec et al., 2019). DMH may also be involved in behavioral thermoregulation and cold-seeking behavior (Almeida et al., 2006).

The RPa is the final key relay that controls the sympathetic outflow to the thermoregulatory organs. This region is connected to the brown (Cano et al., 2003) and white adipose tissue (Nguyen et al., 2014), to the heart (Standish et al., 1995), to the skeletal muscle (Billig et al., 2001), to the liver (Kalsbeek et al., 2004; Ter Horst et al., 1993), to the thyroid (Kalsbeek et al., 2000), to the adrenergic cells in the adrenal gland (Morrison and Cao, 2000), to the bones (Dénes et al., 2005), to the bone marrow (Dénes et al., 2005), and to the kidney (Huang and Weiss, 1999). Functionally, RPa neurons control brown adipose tissue (Morrison et al., 1999), shivering (Nakamura and Morrison, 2011), and cutaneous blood vessels (Cerri et al., 2010; Meyer et al., 2017).

This main circuit, going from the PBN to the RPa is modulated by many other brain regions, that can amplify or reduced the central outflow to the thermal effectors. For instance, an area such as the Suprachiasmatic Nucleus (SCN) receives the retinal information that maintains the circadian oscillation of body temperature, even if non-SCN projecting retinal ganglion cells have recently been reported to play a role (Rupp et al., 2019); the orexinergic neurons in the Lateral Hypothalamus may drive the necessary increase in temperature and metabolic rate that the state of arousal requires (Cerri et al., 2014), and may also be linked to thermogenesis (Tupone et al., 2011), although may be not involved in torpor (Lo Martire et al., 2020); the Nucleus of the Solitary Tract (NTS) may convey information regarding the amount of oxygen available in the bloodstream (Madden et al., 2017). The activity of this central circuit could be modulated in many ways to induce states resembling torpor, since it has been shown that the direction of the changes in body temperature in response to changes in ambient temperature can even be reversed (Tupone et al., 2017).

Effective procedures inducing synthetic torpor through the manipulation of the thermoregulatory network

Inhibition of neurons within the RPa

The RPa plays a key role in controlling body temperature. As far as we currently know, there are no pathways from other regions of the brain that bypass the RPa in conveying information to the rest of the body. The RPa is therefore an obligatory relay that reverberates the commands from the higher center to the sympathetic preganglionic neurons within the Lateral Horn of the spinal cords. The activation of neurons within the RPa, by excitation of disinhibition, leads to an increase in thermogenesis (Morrison et al., 1999) and to a reduction in heat dissipation (Cerri et al., 2010). At thermoneutrality, RPa neurons are tonically active, providing a basic drive to the preservation of body temperature (Cerri et al., 2010; Zaretsky et al., 2003). Inhibiting these neurons leads to a transitory reduction in body temperature and an increase in heat dissipation. It is therefore reasonable that, to enter torpor, the activity of RPa neurons must be switched off (Frare et al., 2018; Hitrec et al., 2019).

Prolonged inhibition of neurons within the RPa was shown to induce a deep hypothermic state resembling natural torpor as regards many features (Cerri et al., 2013). RPa neurons are key in controlling the general metabolic state of the body, and any method of central induction of Synthetic Torpor will, directly or indirectly, affect these neurons.

RPa inhibition requires a neurosurgical approach. The procedure, by itself, now has the potential to be very straightforward in humans. The use of frameless stereotaxic technology together with virtual neuronavigation would allow a neurosurgeon to carry out the entire procedure in a short time. This would make this technology usable as an "elective procedure" in clinical settings, but its use in emergency conditions would have to be evaluated.

Adenosine A1 receptor activation

A1R activation by N6-cyclohexyladenosine (CHA) was shown to induce a deep hypothermic state in rats (Shimaoka et al., 2018; Tupone et al., 2013), and the target region seems to be the NTS. The activation of NTS neurons was shown to inhibit brown adipose tissue thermogenesis (Madden and Morrison, 2005), thus making them

a sensitive target for the induction of hypothermia. The physiology of adenosine-induced synthetic torpor appears slightly different from that observed in regular hibernators (Swoap et al., 2007). Considering that the site of action of CHA was shown to be the NTS, it is possible that CHA activates the diving reflex (Hult et al., 2019; Silvani et al., 2018), a still effective way to reduce oxygen consumption, but with different cardiovascular features. However, adenosine has been shown to be involved in the regulation of hibernation (Drew et al., 2017; Frare et al., 2019); consequently, the actual mechanisms of action are yet to be understood in detail.

The use of systemic CHA has been coupled with temperature target management (Bailey et al., 2017), and with the use of an adenosine receptor antagonist (Jinka et al., 2015), to counteract the intrasubject difference in CHA response and to reduce the cardiovascular side effects, so far with encouraging results.

Further potential approach to synthetic torpor

Inhibition of skin cold receptors

To prevent body temperature from dropping, skin cold receptors activate thermogenesis when the core body temperature is still within a normal range. A pharmacological blockade of their activity may cause the activation of thermogenesis to be prevented, inducing a reduction in body temperature (Feketa and Marrelli, 2015). Among the most relevant cold receptors, TRPM8 seems to play a major role (Babes et al., 2010), and the use of a TRPM8 antagonist is effective in inducing a state of moderate hypothermia in rodents (Almeida et al., 2012). Considering that the exposure to a warm temperature also promotes a reduction in metabolic rate and thermogenesis (Grimpo et al., 2013), combining the inhibition of cold sensing with the activation of warm receptors may be a useful synergic combination.

Exploitation of the skin temperature afference

The PBN receives the thermal information from the skin in two separate regions for cold (Nakamura and Morrison, 2008) and for warmth (Nakamura and Morrison, 2010). Neurons within the lateral PBN have been shown to have intrinsic thermosensitivity (Xu et al., 2019; Xue et al., 2016) and a genetic fingerprint (Geerling et al., 2016), representing a possible new target for the induction of a state of synthetic torpor. Since seasonal hibernators maintain their body temperature well above the temperature of the hibernaculum (Lee et al., 2009), animals in hibernation seem to preserve thermoregulation (Florant and Heller, 1977). Such a response seems to be mainly caused by activation of a central command (Heller and Colliver, 1974; Williams and Heath, 1971), so it is not clear whether the PBN thermosensitive neurons could play a role. Nevertheless, a drug acting selectively on these neurons may be able to induce a safe state of hypothermia.

Exploitation of Hypothalamic thermosensitivity

Warm and cold sensitive neurons within the POA of the hypothalamus play the role of the conductor in commanding the orchestra of thermal effectors (Amici et al., 2014; Tabarean, 2018; Tan et al., 2016). Their intrinsic thermal sensitivity can be a target for the modulation of the central thermoregulatory drive. The molecular mechanisms driving intrinsic thermosensitivity are not yet completely known. It has been suggested that changes in ionic current are responsible for thermosensitivity (Boulant, 1998; Griffin et al., 1996), but much is still to be understood (Zhao and Boulant, 2005). Pharmacological activation of different opioid receptors have been shown to modulate the degree of thermal sensitivity in POA neurons in slices (Xin and Blatteis, 1992; Yakimova et al., 1998, 1996), and to induce hypothermia in rats (Yakimova and Pierau, 1999). On these bases, it is indeed interesting that naloxone can arouse the hamster from torpor (Margules et al., 1979), since endogenous opioid has been reported to

play a key role in regulating hibernation (Beckman and Llados-Eckman, 1985; Cui et al., 1993; Oeltgen et al., 1982; Tamura et al., 2012).

An interesting physiological state characterized by the loss of the intrinsic thermosensitivity of the POA warm and cold sensitive neurons is REM (Parmeggiani, 1986). Cooling of the POA during REM sleep fails to induce the increase in metabolic rate observed when the same stimulation is applied during wakefulness or NREM sleep (Glotzbach and Heller, 1976). Direct recording of POA temperature-sensitive neurons during sleep confirms the loss of thermosensitivity (Alam et al., 1995; Glotzbach and Craig Heller, 1984; Parmeggiani et al., 1987). Interestingly, hypothermia is not observed during REM sleep, a state that is, on the contrary, characterized by an increase in brain temperature (Parmeggiani, 2007); nevertheless, this peculiar lack of central thermosensitivity may be an interesting model for synthetic torpor research, since it also appears to be specific to thermoregulation and not in place for other types of physiological regulation (Luppi et al., 2010). The POA has also been shown to participate in the hypothermic effect of other drugs, such as lithium (Jones et al., 2008).

NREM sleep also has a reciprocal relationship with thermoregulation (Harding et al., 2019; Szymusiak, 2018). Preoptic neurons, in fact, mediate the heat loss that characterizes NREM sleep (Harding et al., 2018; Kroeger et al., 2018; Zhao et al., 2017). NREM sleep was proposed to be a "small torpor", since it shares many features with torpor (Silvani et al., 2018).

Within the hypothalamus, the SCN is the master clock of the organism, dictating the circadian oscillation in body temperature (Saper et al., 2005). SCN neurons were also shown to be intrinsically thermosensitive (Burgoon and Boulant, 2001), making them a possible target for body temperature regulation. The direct input that from the retina hits the SCN neurons could open possibilities for some kind of enhanced light therapy (Rupp et al., 2019).

Interestingly, a change in central thermal sensitivity may be something that could justify the change in thermal balance experienced even at rest by astronauts, something called "space fever". An increase in body temperature in astronauts was in fact described during both short (Dijk et al., 2001; Gundel et al., 1997, 1993) and long missions (Stahn et al., 2017). To explain this effect, two hypotheses may be put forward. The first is based on the reduced efficiency of heat loss mechanisms through evaporation and convection (Fortney et al., 1998; Polyakov et al., 2001). This could explain the yet-unexplained systemic vasodilation described in astronauts (Norsk et al., 2015). The second one is based on the idea that the central thresholds for warm defense may be lowered by permanence in space, an effect possibly mediated by inflammatory cytokines (Stahn et al., 2017). This last hypothesis may also explaine the fact that body temperature was reported to be elevated even after the return to Earth (Stahn et al., 2017). Sleep deprivation, and fragmentation, often occurring in space (Dijk et al., 2001; Gundel et al., 1997, 1993) may also contribute to the increase in body temperature (Vishwakarma et al., 2020).

Exploitation of the mechanism of Motion sickness

A peculiar condition that may affect thermoregulation by inducing hypothermia is motion sickness (Nalivaiko, 2018). The mechanism behind the kinetosis-induced hypothermia is not yet known. An increase in thermal dissipation was reported as a possible cause (Del Vecchio et al., 2014; Ngampramuan et al., 2014). Since kinetosis is an almost physiological state, it is an interesting model of study that could unlock new interesting pharmacological targets. For instance, endocannabinoids, besides being involved in the modulation of phenotype during hibernation (Mulawa et al., 2018), were shown to play a role in the appearance of motion sickness in people on parabolic flight, where a significant decrease in the blood levels of anandamide characterized subjects with motion sickness compared with subjects who did not experience it (Choukèr et al., 2010; Strewe et al., 2012). Although a reduced activity of the endocannabinoid system may be related with the appearance of motion sickness, hypothermia belongs to the classic tetrad of effects of molecules with cannabinoids property (Lynes et al., 2019; Metna- Laurent et al., 2017). The cannabinoids receptor CB1 seems to be the one involved in the thermal effects of cannabinoids (Metna-Laurent et al., 2017), although recent evidence may also suggest the involvement of other mechanism (Gamage et

al., 2020). Whether the thermoregulatory effects of cannabinoids are mediated by the central nervous system, by other organs, or by both is still unclear (Boon et al., 2014; Cardinal et al., 2015, 2012; De Azua et al., 2017; Pertwee et al., 1991; Quarta et al., 2010).

Beside anatomical targets, nutrition may also open the way to facilitating synthetic torpor, since it plays a relevant role in naturally-occurring torpor (Ruf and Arnold, 2008), and also in sleep regulation (Luppi et al. 2014). Hibernators were in fact shown to favor some n-6 polyunsaturated fatty acids (PUFA), and in particular the linoleic acid (Giroud et al., 2013), together with a selective mobilization and utilization of lipid (Giroud et al., 2019). Interestingly, while n-6 PUFA enhance torpor expression, the opposite was shown with n-3 PUFA, (Vuarin et al., 2016). Among the n-6 PUFA, linoleic acid may play a very relevant role. The amount of this fatty acid in the cell membranes can be a relevant factor in determining the degree of the decrease in body temperature during torpor, since it may help maintaining the functionality of the SERCA pump in the heart at low temperature. (Giroud et al., 2018b, 2013). Moreover, since PUFA work as precursors of the eicosanoids, they could affect the inflammatory status during hibernation (Giroud et al., 2018a). All this evidence point to a relevant role of nutritional status in modulating the phenotype of torpor, a role that needs to be evaluated carefully. At present, no study has investigated whether PUFA promote an increase in safety during synthetic torpor, but future studies on this matter are necessary to evaluate the potential use of diet supplements in such condition.

TESTING HIBERNATION "IN THE FIELD": THE ROLE OF THE INTERNATIONAL SPACE STATION

The main approaches that could be used to induce synthetic torpor in non-hibernators have been described above, but a comprehensive description of all the possible compounds goes beyond the scope of this article. Research into other mechanisms, and other drugs (Jones et al., 2008), may provide further insights. The multiple methods that are being tested and the growing interest in this topic provide a reasonably optimistic hope that a synthetic torpor technology will be available in the next few decades. This is especially true considering that hibernation research for space applications is at a stage in which it will greatly benefit from the opportunity to run experiments "in the field". To this aim, we propose hosting a few seasonal hibernators housed in a dedicated cage on board the ISS for several months. The cage will have to be fully automated, in terms of providing the animals with the most comfortable environment to enter hibernation, and in terms of monitoring animals' physiological parameters (such as oxygen consumption, infrared emissions, motor activity, and more). A similar device was already designed and used in recent years, and could be the base for the construction of un updated model. (Cancedda et al., 2012)The state of the animals after returning to Earth will provide an enormous and critical amount of information that will be precious in developing countermeasures to two of the more severe effects of long-term performance in microgravity: muscle weakness and radiation damage. Besides animal studies, the ISS is also a key location to investigate many physiological correlates of torpor. For instance, the mechanism of space fever is still unknown, and a clear understanding of the impact that microgravity and radiation have on both autonomic and behavioral thermoregulation will be necessary before venturing into synthetic torpor territory. This will also require the development of new and reliable ways to measure body temperature in different districts of the body (Gunga et al., 2008; Opatz et al., 2013).

The evaluation of the endocrine response should also be another important field of investigation. How the stress of isolation can affect the response of astronauts to microgravity and its interplay with neuroendocrine systems potentially involved in torpor, such as the endocannabinoid system, should be objects of dedicated experiments. Experiments conducted on Earth already shown how relevant this factor is (Feuerecker et al., 2019; Strewe et al., 2018), but little we know on the effect that a prolonged state of hypometabolism may have on the stress response.

The use of the ISS as an experimental station for torpor research may also face some problems. The number of experiments that would need to be planned and organized is high, and many of them would interplay with each other. Many experts in many different fields of science are also necessary to tackle the issue effectively, without wasting precious time and resources in isolated experiments with no long-term vision. We feel that, aside competitive grant, the creation of a governments funded division, or, even better, of a dedicated institute, that could group and coordinate all the excellent scientists who are already working in the field, would be a necessary step towards the ambitious goal of synthetic torpor exploitation. Such an entity could effectively interact with the private sector to develop the necessary technology, gather specialists from other fields when needed, and be a pivot to accelerate the rate of discovery in the field, paving the way to an effective colonization of space.

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Legends

Figure 1 shows an illustrative drawing of the central thermoregulatory network. Blue lines = Cold sensing pathways; Red lines = Warm sensing pathways; Yellow lines = Modulatory pathways

Figures

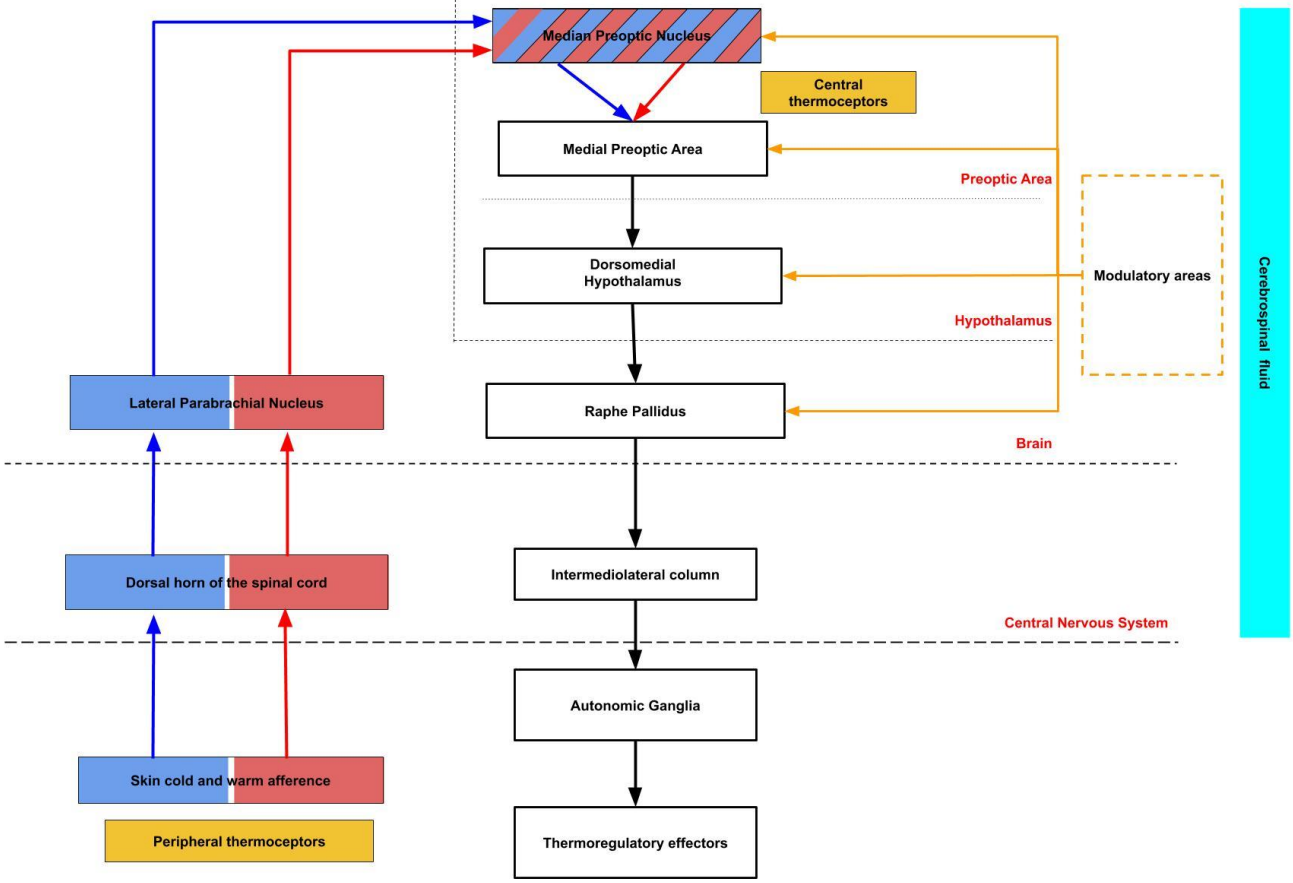
Median Preoptic Nucleus
Central thermoceptors
Medial Preoptic Area
Preoptic Area
Dorsomedial Hypothalamus
Modulatory areas
Hypothalamus
Cerebrospinal fluid
Lateral Parabrachial Nucleus
Raphe Pallidus
Brain
Intermediolateral column
Dorsal horn of the spinal cord
Central Nervous System
Autonomic Ganglia
Skin cold and warm afference
Peripheral thermoceptors
Thermoregulatory effectors

Figure 1

Figure 1