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REVIEW ARTICLE

Seasonal Control of Mammalian Energy Balance: Recent Advances in the Understanding of Daily Torpor and Hibernation

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Endothermic mammals and birds require intensive energy turnover to sustain high body temperatures and metabolic rates. To cope with the energetic bottlenecks associated with the change of seasons, and to minimise energy expenditure, complex mechanisms and strategies are used, such as daily torpor and hibernation. During torpor, metabolic depression and low body temperatures save energy. However, these bouts of torpor, lasting for hours to weeks, are interrupted by active 'euthermic' phases with high body temperatures. These dynamic transitions require precise communication between the brain and peripheral tissues to defend rheostasis in energetics, body mass and body temperature. The hypothalamus appears to be the major control centre in the brain, coordinating energy metabolism and body temperature. The sympathetic nervous system controls body temperature by adjustments of shivering and nonshivering thermogenesis, with the latter being primarily executed by brown adipose tissue. Over the last decade, comparative physiologists have put forward integrative studies on the ecophysiology, biochemistry and molecular regulation of energy balance in response to seasonal challenges, food availability and ambient temperature. Mammals coping with such environments comprise excellent model organisms for studying the dynamic regulation of energy metabolism. Beyond the understanding of how animals survive in nature, these studies also uncover general mechanisms of mammalian energy homeostasis. This research will benefit efforts of translational medicine aiming to combat emerging human metabolic disorders. The present review focuses on recent advances in the understanding of energy balance and its neuronal and endocrine control during the most extreme metabolic fluctuations in nature: daily torpor and hibernation.

Key words: daily torpor, hibernation, metabolic suppression, hypothalamus, brown adipose tissue

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Introduction

Energy budgeting is one of the most important aspects for organisms to ensure survival in seasonal environments. In mammalian and avian lineages, the evolution of sustained endothermy has offered many advantages, such as increased motility, brain function, growth rate and reproductive success. However, high metabolic rates require high and costly energy expenditure that must be constrained by an array of strategies permitting rheostasis and the survival of extended periods of energy shortage often associated with seasonal environmental changes. Rheostasis describes the regulation of physiological processes with rhythmically changing set points, as opposed to constant steady states of homeostatically regulated systems. The coordinated down- and up-regulation of metabolism, as performed by a large number of diverse mammalian and avian species, is an especially fascinating phenomenon in this regard (1).

The physiological state of reduced metabolic rate (MR) and body temperature (T_b) in endothermic vertebrates is termed 'torpor'. Torpor is the physiological trait used for a reduction of energy expenditure and enables survival during periods of energy shortage. The

history of torpor research dates back to the beginning of comparative physiology, uncovering extreme cases of reductions in energy use (2). In recent years, torpor has been identified in a progressively increasing number of species from all mammalian subclasses (monotremes, marsupials and placentals) and many avian orders, transforming a formerly taxonomically limited trait into one with broad phylogenetic roots and diversity (1,3).

Torpor is characterised by a pronounced reduction of MR up to 98% of basal MR (4,5). The mechanisms and pathways initialising the drop of metabolic rate are poorly understood, although entrance into torpor, which usually occurs at low ambient temperature (T_a), is generally associated with three major observations. Initially, the euthermic T_b set point is lowered and MR is reduced (6). The reduction of MR results in a fall of T_b because insufficient heat is produced to maintain a high, stable T_b. The fall of T_b in turn causes a further reduction of MR. In some species, particularly in hibernators, reductions in heart and ventilation rates and inactivation of enzymes further reduce MR to a fraction of that observed during euthermia. During torpor, T_b often approaches and follows T_a. Although torpid animals may thermo-conform over a wide temperature range, endothermic thermoregulation is not abandoned. When T_b reaches extremely low values, torpid animals increase metabolism to maintain T_b above a minimum, which varies widely among species, presumably to prevent tissue damage.

Torpor frequency, depth and duration differ widely among species, ranging from prolonged periods of seasonal hibernation to short daily bouts of reduced metabolism. Hibernation is characterised by multiday torpor bouts with T_b often between 0 and 10 °C but, in some species from the arctic, it may fall below 0 °C without freezing, even at a measured minimum of −2.9 °C (1,7). Importantly, bouts of metabolic depression in most species are not continuous throughout winter, but multiday bouts of torpor are interrupted by periodic arousals to euthermic MR and T_b values. By contrast, daily torpor is characterised by several hours of reduced metabolic rate and T_b, usually during the rest phase of the 24-h (nycthemeral) activity rhythm (Fig. 1). In some species, such as in desert-dwelling spiny mice (*Acomys* sp.), daily torpor can be extremely shallow at high T_a, yet MR decreases significantly (8). This phenotype is phylogenetically widely distributed because hibernating pygmy possums (*Cercartetus nanus*) display similar reductions of MR at high T_a with only a minor reduction in T_b (9). Between these two extremes, there is an entire scale of different torpor depth and duration, including hibernation at high T_b, as found in bears or aestivation in Madagascan lemurs (10–12). However, species expressing exclusively daily torpor (i.e. daily heterotherms) differ significantly from hibernators that are physiologically capable of expressing multiday torpor with lower minimum T_b and minimum MR (1). As noted above, although, in many heterothermic species, T_b may track T_a, T_b at any stage during torpor can be controlled. The actual T_b values depend on T_a, body mass (surface-to-volume ratio) and torpor bout duration and the degree of metabolic depression. Hence, torpid animals clearly remain endotherms because they can alternate between a euthermic tachymetabolic state and a torpid bradymetabolic state with largely reduced body functions and can even use endothermic thermoregulation when torpid (4,5).

Cellular, biochemical and molecular adaptation during torpor

Although the biochemical changes underlying metabolic depression during torpor have yet not been resolved, a limited number of studies suggest rather general reductions of cellular metabolism in torpid states. These studies focus on the depression of metabolic pathways (such as glycolysis), transcription, translation and protein degradation (13–17). Thus, it appears that cellular metabolism is reduced in general and cell proliferation/differentiation is halted during torpor. A recent molecular survey of the genetics and proteomics during torpor showed that new genes or different proteins are not required for the expression of torpor. Instead, the phenotype of torpor may solely be related to the regulation of common metabolic pathways (18).

With reduced energy budgets, cellular homeostasis has to be maintained to counteract entropy. Thus, sufficient energy production in form of ATP is required to maintain ion homeostasis, renew proteins and decrease cellular damage. Clearly, the cellular energy consumption processes require substantial reduction and, in some cases, this is caused by the reduction of temperature and enzyme activities. Mitochondria are central organelles in the conversion of

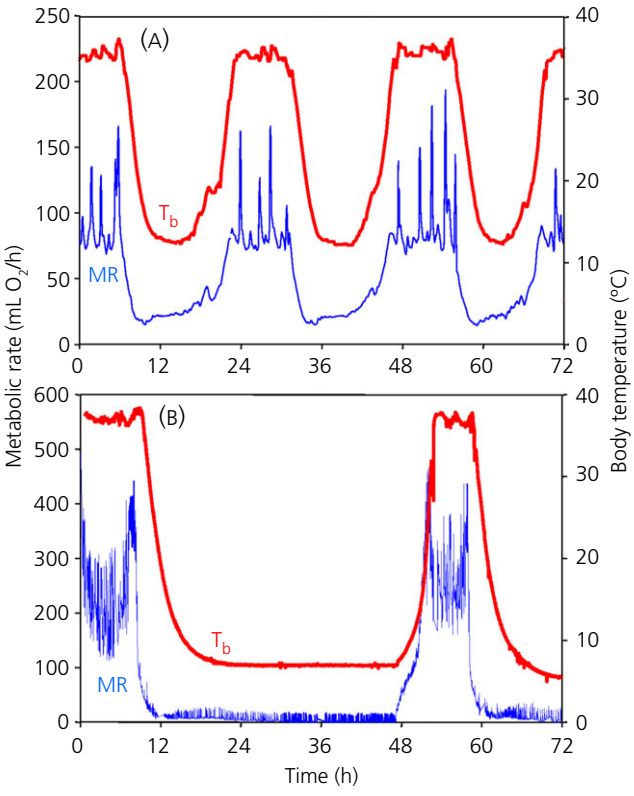

Fig. 1. Torpor episodes in daily torpor and during hibernation. T_b, body temperature; MR, metabolic rate. (A) Spontaneous daily torpor in short-day acclimated Djungarian Hamster, *Phodopus sungorus*, at 5 °C ambient temperature and food *ad libitum*. (B) Torpor bout during hibernation in a common dormouse, *Glis glis*. In *Glis*, the metabolic rate was recorded at high resolution to visualise intermittent ventilation in the torpid state.

nutrient to cellular energy (ATP). Temperature passively controls mitochondrial energy conversion through Q_{10} effects, although there is evidence for additional active metabolic depression that persists in isolated mitochondria from hibernating artic and thirteen-lined ground squirrels (*Spermophilus parryii*) and in torpid Djungarian hamsters (*Phodopus sungorus*) (19–22). Mitochondrial substrate oxidation is reduced during hibernation and this appears to be controlled by succinate dehydrogenase activity and possibly allosteric inhibition (19,23,24). The reduction in mitochondrial ATP production correlates with T_b rather than metabolic rate *per se* (21,25).

Seasonal control of torpor

In seasonal hibernators, torpor expression is tightly linked to circannual rhythms. Hibernation is often obligatory and includes a preparation phase (pre-hibernation fattening, migration to or selection of hibernacula) with complex changes in food choice (e.g. reduction of protein intake, increased consumption and selection of specific fatty acids) and anatomy (e.g. reduction of digestive tract and reproductive organs) (26–32). The reduction of behavioural activities together with the low MR during torpor bouts reduces energy requirements during the hibernation season by up to 95% (5).

The use of daily torpor is more flexible and can either occur spontaneously (in the presence of available food), in a seasonal context or, optionally, in response to energetic challenges such as food shortage or cold exposure. Daily torpor usually occurs during the resting phase of the circadian cycle and reduces daily energy requirements, as measured in captivity, by up to 60% (33). However, recent evidence from the field suggests that daily torpor may also be used to restrict foraging times to only a few hours per day in the early evening, with torpor bouts lasting for most of the day. Together with passive rewarming in the sun, this reduces daily energy expenditure by up to 80% (34,35).

In contrast to hibernation, when behaviour usually is minimised, although not entirely absent, daily torpor enables maintenance of the social, territorial and foraging activities of a small mammal (5,36). Behavioural activities and ecological significance have been studied in detail and are reviewed elsewhere (37,38). Here, we focus on the seasonal control of metabolism by the central nervous system (CNS) and brown adipose tissue, as well as endocrine adjustments that occur in peripheral tissues.

CNS control

Despite the general depression of cellular metabolism during torpor including silencing of cortical electroencephalogram patterns, functional brain activity persists. The specific environmental cues for the induction of torpor are still not fully understood. However, torpid animals are able to perceive and respond to external stimuli, including olfactory stimulation, precisely regulate their T_b and regularly arouse from torpor (39). Hence, the brain requires functional sites and pathways that regulate these processes, as well as protective mechanisms to ensure that tissues remain undamaged during torpid states. Changes in gene expression have been observed in the brain during deep hibernation and these show extreme regional and temporal differences, providing important information about general adaptive mechanisms during torpor (40,41). However, to date, few studies have focused on precise anatomical information of hibernating brains to identify the neuronal networks and pathways involved in the control of torpor (42,43). Current state of knowledge suggests that the hypothalamus plays an instrumental and central role in controlling torpor.

The hypothalamus is the area of the CNS that links the nervous system to the endocrine system and coordinates the majority of autonomic responses (44). This includes regulation of thermal and metabolic processes, circadian organisation, sleep and reproduction. Available data suggest that various hypothalamic nuclei are involved in the control of both hibernation and daily torpor. Neurones of the preoptic area, a major thermoregulatory centre, are activated during entrance into deep torpor in thirteen lined ground squirrels (*Ictidomys tridecemlineatus*), as well as pharmacologically induced torpor-like states in Djungarian hamsters (42,45,46). This is clear evidence for the maintenance of active thermoregulatory processes during torpor. Indeed, studies in marmots (*Marmota flaviventris*) provide *in vivo* evidence that thermosensory and thermoregulatory mechanisms remain functional during hibernation but progressively change to a lower setpoint (47,48).

Moreover, the suprachiasmatic nuclei (SCN) that control circadian rhythms remain active during hibernation and daily torpor, as measured by expression of the immediate early gene *c-fos* (42,46,49,50). The role of the circadian clock in torpor control has been subject of many studies, although its mechanisms have not been fully resolved and appear to differ substantially among species and torpor patterns (51). Spontaneous daily torpor is strongly controlled by the circadian clock and often occurs during the resting phase of an animal. In Djungarian hamsters, the molecular clockwork remains largely intact during torpor and lesion studies of the SCN provide evidence that the clock is involved in the timing of daily torpor bouts (49,52,53). Studies of deep hibernators are more controversial because they are complicated by the experimental timing during the hibernation season, thus providing evidence for, as well as against, active timekeeping by the circadian system (54–63). A single study investigating molecular clock mechanisms directly in the SCN during deep torpor in European hamsters (*Cricetus cricetus*) shows that the molecular clockwork stops, questioning its regulatory role in timing, at least through classical clockwork mechanisms (50). However, increasing *c-fos* expression in the SCN with increasing torpor bout duration in these hamsters indicates some involvement in periodic arousal mechanisms (42,50).

Daily torpor in small mammals often occurs as an immediate response to food withdrawal, suggesting that the central nervous circuitry involved in food regulation may also play an essential role in torpor induction. The arcuate nucleus of the hypothalamus (ARC) regulates food intake and energy expenditure via anorexigenic (pro-opiomelanocortin/cocaine- and amphetamine-regulated transcript) and orexigenic [neuropeptide Y (NPY)/agouti-related protein] neuronal populations. When a daily torpor-like state is induced by injections of a glucose analogue that disrupts glucose oxidation (2-deoxy-glucose) in Djungarian hamsters, ARC neurones are

activated. Hence, they appear to sense the lack of fuel caused by glucoprivation (46). Moreover, ARC lesions are able to prevent spontaneous daily torpor in this hamster, although torpor bouts or torpor-like bouts can be reinstated by fasting or 2-DG injections (64). Studies investigating potential ARC mechanisms regulating torpor suggest that the torpor response is mediated through NPY and NPYY1 receptor signalling (43,65,66). Interestingly, during deep hibernation, ARC neurons remain silent throughout the entire torpor bout in thirteen lined ground squirrels, although they are activated during inter-bout arousals (42). This suggests that thirteen lined ground squirrels experience hunger during this state, although they do not eat even if food is available. Whether it is an ARC signal that eventually induces the subsequent torpor bout remains unknown. Taken together, the ARC appears to sense the energetic state of the animal and, in turn, is able to influence torpor expression. Whether this is the case in fasting induced torpor only or also in spontaneously occurring torpor remains unclear.

Microarray studies suggest that seasonal body weight changes in Djungarian hamsters or photoperiodic rats (F344) are not associated with gene expression changes observed in classical ARC systems but involve distinct mechanisms and structures (67–69). Hence, long-term seasonal body weight changes do not reflect energetic deficit. Instead of common ARC mechanisms, other structures have been identified as central players in the seasonal regulation of body weight: the dorsomedial posterior arcuate nucleus and the tanycytes. Because these structures appear to be important mediators of seasonal adaptations in energy balance, they are also interesting regions of the hypothalamus for involvement in torpor regulation.

The tanycytes adjacent to the third ventricle comprise a small cell population in the brain that is strongly activated during the late torpor and early arousal states of hibernating thirteen lined ground squirrels (42). Tanycytes are a specific type of glial cell that can bridge the ventricle to hypothalamic nuclei and sense and integrate the energetic state of the animal (70). This observation is particularly interesting because tanycytes have been identified as major players in seasonal changes of body mass and reproduction in birds and mammals by regulating thyroid hormone (T3) availability to the hypothalamus (71–73). In the Djungarian hamster, the seasonal reduction in tanycyte derived T3 and, consequently, T3 availability to the hypothalamus is clearly critical to permit seasonal torpor (74,75). The mechanism by which a reduction in hypothalamic T3 is permissive to torpor is unknown but, as a transcriptional regulator, it likely involves transcriptional changes of one or more genes. The orphan receptor *gpr50* represents one putative candidate. *Gpr50* knockout mice show enhanced propensity to fasting-induced torpor (76). *Gpr50* is highly expressed in tanycytes of long-day housed Djungarian hamsters and down-regulated upon short-day exposure (77). Whether photoperiod induced suppression of this receptor is a requirement for torpor permissiveness in Djungarian hamsters is an intriguing question. There could be a role for the temporally defined period of *gpr50* expression found from late July to early September, prior to torpor use in early winter in hamsters housed under natural photoperiod (78). Moreover, there is evidence to suggest that retinoic acid signalling in tanycytes mediates seasonal responses in food intake and body weight through hypothalamic actions in Djungarian hamsters and photoperiodic rats (68,79–81). Generally, retinoic acid signalling is increased during the summer photoperiod (i.e. the time of somatic growth and fattening) and reduced during the winter photoperiod. Whether retinoic acid signalling is involved in torpor regulation remains to be revealed.

Tanycytes have emerged as potential nutrient sensors in the hypothalamus (82). Consistent with the role of tanycytes in nutrient sensing, thioredoxin-interacting protein (*txnip*), an important cellular metabolic regulator of cellular lipid and glucose metabolism is highly expressed in these cells (76,83,84). *Txnip* gene expression in tanycytes is up-regulated by fasting, and further induced in fasted *gpr50* null mice and fasting-induced torpor (76). Furthermore, overexpression of *txnip* in the medial basal hypothalamus of mice facilitates features of the torpid state (i.e. reduced oxygen consumption, respiratory quotient, physical activity and brown adipose temperature) (83). Consistent with a role in torpor, *txnip* is induced only in short-day torpid hamsters (76). Taken together, the current data suggest that tanycytes are likely to be involved in the preparation and the acute regulation of torpid states.

Brain control of the sympathetic nervous system (SNS) activity plays a leading role in thermoregulation and may also contribute to the regulation of torpor. In nonhibernators, the raphe nuclei in the brain stem have been identified as a major relay station between higher brain areas and sympathetic output, mediating vasomotor responses and controlling thermoregulatory heat production in brown fat (85,86). Whether this pathway is identical in hibernators remains to be revealed. The importance of the SNS in torpor, however, has been clearly demonstrated. Together with the antagonistic parasympathetic vagus system, the SNS regulates blood flow and metabolic rate of peripheral organs and is strongly involved in torpor initiation, torpor maintenance and arousal. Surprisingly, sympathetic activity is enhanced for the initiation of torpor bouts, once more emphasising that torpor is an active rather than a passive state (87–89).

In summary, the collection of studies on brain and torpor suggest that the hypothalamus plays a complex role in torpor regulation by integrating and regulating thermal and metabolic processes, although we are far from a complete understanding of the involvement of different nuclei and pathways involved.

Central control and peripheral action of thermoregulation

Mammalian endothermy requires distinct sites of thermogenesis, which have to be controlled centrally to maintain body temperature. Two major forms of thermoregulatory heat production are used in mammals: shivering (uncoordinated small muscle contractions) and nonshivering thermogenesis (NST). The classical site of NST in eutherians is brown adipose tissue (BAT). BAT executes adaptive NST maintaining T_b in lower ambient temperatures (90). Furthermore, heat production from BAT assists in re-warming processes from torpid states (91). BAT thermogenesis is controlled by a dense innervation of sympathetic nerve fibres descending from the CNS (92,93). Released noradrenaline acts mainly via β3 adrenergic

receptors inducing lipolysis and stimulation of mitochondrial oxidation rates. High energy turnover is catalysed by the mitochondrial uncoupling protein 1 (UCP1) that uncouples respiration from ATP production by short-circuiting proton currents over the mitochondrial inner membrane. UCP1 is regulated at multiple levels: mRNA transcription is stimulated by complex hormonal (e.g. T3) and chronic sympathetic innervation, while UCP1 protonophoric function is directly controlled by free fatty acids and purine nucleotides.

Thermogenically competent BAT is found in eutherian mammals but not in in marsupials and birds, although there is some evidence for adaptive NST in these groups. Even in some eutherians (e.g. pigs), the gene for UCP1 is inactivated, resulting in poor thermoregulation. These endotherms may rely on alternative NST mechanisms, with some of those being recently discovered in UCP1-ablated mice. The physiological control of alternative heat sources in muscle and white adipose tissue is not yet understood, requiring further confirmative studies (94,95).

Endocrine seasonal control

An increasing body of evidence sheds light on the endocrine signalling of metabolic depression. In most hibernators, pronounced changes in physiological parameters such as body mass, reproductive axis or thermal insulation precede the torpor season. These are caused by, or are associated with altered hormonal states, which are prerequisites for seasonal torpor. For example, the role of melatonin in seasonality is well-documented. Melatonin secretion from the pineal gland precisely reflects night length and is used by seasonal species to time seasonal events including torpor expression (96,97). The melatonin feeds back to the brain via the pars tuberalis of the pituitary gland that possesses a large number of melatonin receptors in seasonal and nonseasonal species (98). A decreased duration of melatonin release in summer permits thyroid-stimulating hormone β release from the pars tuberalis, which in turn increases the expression of type II deiodinase (*Dio2*) in the tanycytes. *Dio2* encodes for the enzyme converting thyroxine (T4) to the bioactive triiodothyronine (T3) that is a crucial driver of seasonal adaptations in birds and mammals (71–73). Although changing day length and light period alter the melatonin and downstream signal, this consequently leads to very diverse physiological adaptations in various species. There is also an array of peripherally secreted hormones that feedback to the brain on the metabolic status of the body. Most of these hormones induce behavioural and physiological changes in the brain such as appetite and thermoregulation. Many hibernators such as bats, marmots, ground squirrels or bears fatten in autumn to survive on fat stores over the winter (27). The enlarged fat stores release elevated leptin concentrations that peak at the beginning of the hibernation period. Furthermore, leptin resistance is considered to be developed during pre-hibernation to counteract its anorexigenic and catabolic effects, thus allowing small hibernators to store fat at maximal amount considering their body size (99–101). Interestingly, injection of leptin, indicating large fat stores, reduces depth and duration of daily torpor (102). By contrast, the concentration of the gut-produced orexigenic hormone ghrelin gradually increases during summer to reach high values at the autumnal-hyperphagic period (27). Peripheral injections of ghrelin cause the increase in food intake at all seasons, even in aphagic hibernators at the start of hibernation (103). In particular, in the grey mouse lemur, it was reported that ghrelin promotes fat accumulation after periods of chronic food deprivation in winter. Plasma levels of ghrelin were positively associated with body mass gain during re-feeding (104). Conversely, levels of peptide YY, an anorexigenic hormone that belongs to the PP-fold family (promoting fat use), were negatively correlated with body mass gain in the same individuals in winter. Ghrelin was also implicated in thermoregulation because peripheral ghrelin injection results in deeper (lower T_b) and more robust torpor bouts of mice, *Mus musculus* (105). This effect could be abolished by ablation of the ARC. Interestingly, the anorexigenic hormone glucagon-like peptide 1 (GLP-1) associates positively with torpor depth in food-restricted mouse lemurs (*Microcebus murinus*) in the summer but not in winter (104). However, regulation of torpor by GLP-1 does not involve NPY neurones because i.c.v. injections of GLP-1 in the ARC did not alter NPY mRNA levels, in contrast to observations made in fasted mice (106).

By contrast to the usually extensive fattening in hibernators for winter survival, small mammals such as the Djungarian hamster, shrews and voles use the opposite strategy, a loss of body mass before winter season, thus saving on absolute energy expenditure (107,108). A reduction of fat mass leads to low levels of circulating leptin, which may be permissive for daily torpor expression, at least in dunnarts (*Sminthopsis macroura*) and Djungarian hamsters (102,109).

A reduced body mass in winter also comprises the reduction of lean mass and the inhibition of growth. Interestingly, pharmacological inhibition of the growth axis strongly impacts on torpor behaviour in Djungarian hamsters (110). A recent study with long acting somatostatin receptor agonists administered i.p. indicates a potential role for somatostatin in the induction of torpor. Pasireotide, a somatostatin receptor (SSTR) subtype 5 agonist, increased the propensity to torpor in short-day acclimated Djungarian hamsters from two to three bouts per week to almost a daily occurrence. Furthermore, pasireotide prolonged the duration of torpor, which, in some hamsters, occasionally extended into the dark phase of the circadian cycle when, under natural conditions, torpor would have ceased (110). However, octreotide a SSTR2 agonist, was almost ineffectual. Because pasireotide does not cross the blood–brain barrier, pasireotide must act at a peripheral site to enhance entry into torpor. The effect of pasireotide to reduce growth would favour the pituitary as the site of action and a possible neuroendocrine involvement, although an indirect action via other peripheral sites or a direct effect of the agonist on BAT cannot be dismissed (111). The ability of pasireotide to increase the propensity of torpor may indicate the role of somatostatin in short-day induced torpor. Although causality has not been established to date, somatostatin is the only neuropeptide found to be increased in the short-day exposed Djungarian hamster in a largely distinct population of neurones in the arcuate nucleus (112).

Decreases of gonadotrophins and gonadal hormones inhibit reproduction during winter in many hibernators. Testosterone can

effectively block daily torpor or hibernation in some but not all species, whereas a lack of testosterone does not induce daily torpor (113,114). Also, prolactin can inhibit daily torpor to some extent (115). At the other extreme, the reproductive system of hibernating bears appears to be in an entirely different state because females give birth and suckle their offspring during the hibernation season (12). Moreover, it appears that many small marsupials and bats use torpor to permit reproduction on limited resources. In some of these species testosterone does not inhibit torpor effectively (116).

The diversity of seasonal strategies in different heterothermic species hampers attempts to draw general conclusions about the hormonal control of torpor. The hormonal status and the interpretation of hormonal signals may differ substantially depending on the ecological and physiological context of each species.

Seasonal control by nutrition and dietary lipids

Dietary lipids have a profound impact on daily torpor and hibernation. Both experimental trials and field studies show that an increased polyunsaturated fatty acids (PUFA) content in the diet and in white adipose tissue reserves is associated with the torpor bout duration and lowers minimal T_b in torpor, thus promoting energy savings (117–121). Linoleic acid (LA) belonging to the *n*-6 family was often the major dietary PUFA provided. However, feeding *n*-6 PUFA-enriched diets did not enhance torpor in all species (122) and, interestingly, diets enriched with *n*-3 PUFA, namely linolenic acid, appear to inhibit torpor expression (123,124).

Enhanced torpor expression mediated by dietary PUFA was linked to a rise of *n*-6 PUFA content and a concomitant reduction of saturated fatty acids (SFA) in lipid reserves as well as in the phospholipid (PL) membranes of almost all body tissues (125,126). The differential distribution of lipid types associated with a varied expression of torpor was also observed independently of dietary manipulation or selection (127–130), suggesting the selective uptake of lipids by the gut or selective utilisation of lipid types during torpor. Indeed, in winter, the grey mouse lemur selectively increases the oxidation of SFA, retaining *n*-6 PUFA (i.e. LA) in body tissues and membranes, at the same time as increasing torpor expression in response to food restriction (131). Such a change in lipid composition is expected to ensure proper body functions at low T_b during torpor. The specific molecular mechanisms by which PUFA affect torpor are entirely unknown to date, although it is possibly not simply a reflection of lipid fluidity.

A potential mechanistic role of PUFA in modulating torpor could be linked to the maintenance of the cardiac function at low T_b (132). Supporting evidence arises from a recent study in Syrian hamsters (*Mesocricetus auratus*) during hibernation showing specific roles of *n*-6 and *n*-3 PUFA in the regulation of the cardiac sarcoplasmic reticulum (SR) calcium ATPase (SERCA), a key enzyme ensuring proper calcium handling and hence heart function (133). Cardiac SERCA activity was positively associated with LA content and negatively with the amount of docosahexanoic acid (DHA) (22:6 *n*-3) in cardiac SR PL of torpid hamsters (133). Moreover, very high amounts of DHA in the SR PL were found in normothermic summer individuals or those that failed to hibernate in winter, as well as in long-day acclimated deer mice (*Peromyscus maniculatus*) that were reluctant to enter torpor, and DHA in muscle tissue was increased by two-fold (124,129,133). Furthermore, it appears that altered SERCA activities determined the minimum T_b reached by Syrian hamsters during hibernation (133). The modulation of SERCA activity may also occur during daily torpor because faster calcium reuptake rates into the SR were found in daily heterotherms (134). Additional work is needed aiming to address the many unknowns concerning *n*-6 PUFA with respect to maintaining body rheostasis during daily torpor and hibernation, particularly in the control of cardiac function.

Conclusions

The seasonal control of energy balance and torpor are amongst the most fascinating physiological adaptations in endotherms. Although comprising a widely used strategy in many mammalian orders, relatively little is known about the mechanisms driving and controlling metabolic depression. Substantial variation in the physiological context and characteristics of torpid states between species complicates the identification of common pathways. Recent advances in the understanding of CNS control over seasonal adaptation in general, fostered by technological progress in analytical methods enabling large scale sensitive and comparative approaches, assists in the dissection of the interplay between environmental and internal factors controlling torpor. Translating the available knowledge from torpor research will benefit many clinical settings that attempt to manipulate metabolism.

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