REVIEW

What can seasonal models teach us about energy balance?

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Abstract

Torpid states are used by many endotherms to save energy during winter. During torpor, metabolic rate is downregulated to fractions of resting metabolic rate and often associated with a severe drop in body temperature that challenges mammalian physiology. Understanding the mechanisms regulating this extreme depression of metabolism bears enormous potential for biomedical research. Torpor behavior has been extensively studied in the Djungarian hamster, also known as Siberian hamster. It is dependent on many preparatory adaptations of physiological and endocrine systems that are likely to be integrated by the hypothalamus eventually controlling metabolism. Although substantial knowledge exists about prerequisites and characteristics of torpor in this species, the cascade of events and their mechanisms of action are not well understood. This review summarizes the current state of knowledge about mechanisms of metabolic regulation in the Djungarian hamster focusing on the potential roles of thyroid hormone and glucose metabolism.

Key Words

- ▶ glucose
- ▶ Siberian hamster
- ▶ tanycytes
- ▶ thyroid hormones
- ▶ torpor

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Introduction

Seasonal mammals have been recognized as intriguing animal models for many physiological processes. Living in seasonally changing environments, these animals have to profoundly adapt morphology and physiology to survive energetic bottlenecks caused by their variable surroundings. Seasonal adaptations include fur changes, readjustment of thermoregulatory capacity and metabolism, precise timing of reproduction as well as pronounced annual body weight cycles and all contribute to one goal: maintaining energy balance during winter. Studying seasonal adaptations of mammals is fascinating because they are very extreme, tightly regulated but also fully reversible. Understanding the underlying regulatory mechanisms will largely contribute to our general understanding of many major physiological processes and has great potential for translational research. Previous reviews have described the respective benefit of examining reproductive and body weight cycles of seasonal mammals (Ebling & Barrett 2008, Dardente *et al.* 2019).

Here, we focus on the annual regulation of torpor, a state of metabolic depression, concentrating on the Djungarian hamster (*Phodopus sungorus*) as animal model.

States of reduced metabolism are used by many endotherms of all mammalian subclasses to cope with energetic bottlenecks such as food or water shortage (Jastroch *et al.* 2016). At high latitudes, times of energy shortage occur regularly and predictably during winter. At this time of year, food resources are limited and at the same time ambient temperature is low; a combination that hampers maintenance of a high body temperature. In response to this energetic challenge, mammals are able to regularly shut down their metabolism to fractions of resting metabolic rate. They can tolerate the resulting severe decrease in body temperature and thereby save large amounts of energy (up to 98%). Different forms of metabolic depression exist, ranging from obligate, deep hibernation, characterized by 96% reduction of

metabolic rate and body temperature close to ambient temperature (-2 to 10°C) for many days, to more flexible strategies such as daily torpor, during which metabolism is only decreased by 75% and body temperature is regulated around 15°C for several hours a day (Heldmaier *et al.* 2004). Deep hibernators disappear throughout winter and remain in their hibernaculum where they undergo multiday torpor bouts that are interrupted by so-called interbout arousals during which the animals rewarm for a short period of time without leaving their burrows. The ultimate reason for these costly arousals remains to be identified, but since they are seen in all endotherms hibernating at low body temperatures, they must serve an important function. As opposed to deep hibernation, daily torpor can be used more flexibly. Metabolism is decreased for only several hours per day, usually during the resting phase of the animal, which allows maintenance of foraging and social activities also during winter (Ruf & Geiser 2015).

Irrespective of the form used, torpid states come along with massive challenges for mammalian physiology:

breathing and heart rate decrease and body temperature falls to low values which leads to reduced transcription and translation rates, at least in the liver (van Breukelen & Martin 2001, 2002). During arousal from torpor, metabolism is switched on rather instantly and reperfusion occurs quickly and vigorously. Despite these challenges that would be detrimental to the human organism, torpid mammals are able to attain, withstand and reverse metabolic and body temperature changes and very precisely control every phase of the torpor bout. Hence, it is likely that the brain is actively involved in torpor control. Although torpor and hibernation have fascinated researchers for a long time and have been described in numerous species, relatively little is known about respective regulatory mechanisms (Jastroch *et al.* 2016). However, understanding regulatory and protective mechanisms of torpor states in mammals has enormous potential for clinical applications. In humans, a controlled reduction of metabolic rate could minimize damage during major surgeries or after traumatic events and could even be used for long-term space flights (Cerri 2017).

Figure 1

Short photoperiod adaptations of Djungarian hamsters. Bars represent the hitherto known time schedule of morphological, physiological and endocrine adaptations (for review see Scherbarth & Steinlechner 2010). The arrows indicate an increase ▲ or decrease ▼ of the respective parameter. T3, tri-iodothyronine; T4, thyroxine.

Daily torpor in the Djungarian hamster

The Djungarian hamster, also known as Siberian hamster, has been extensively studied for its pronounced seasonal adaptations including the use of torpor (Scherbarth & Steinlechner 2010, Cubuk *et al.* 2016). In this species, torpor can be entered either spontaneously in a seasonal context or in response to acute and severe energetic challenges at any time of year.

In a seasonal context, torpor occurs spontaneously and largely depends on other physiological and morphological winter adaptations that have to be completed before the torpor season starts (Fig. 1). Driven by decreasing day length, Djungarian hamsters change fur, regress gonads and lose over 30% body weight in anticipation of energy shortage in winter by voluntary reduction of food intake. After nine to twelve weeks, they start to spontaneously enter daily torpor (Scherbarth & Steinlechner 2010). Daily torpor is initiated by a decrease of metabolic rate to approximately 25% of resting metabolic rate that is followed by a drop in body temperature to values as low as 15°C. The torpid state is maintained for an average duration of six hours, after which the animals arouse and reach normothermia within 30 minutes by non-shivering and shivering thermogenesis (Heldmaier & Steinlechner 1981). In the Djungarian hamster, torpor is timed by the circadian clock and occurs during their resting phase (light phase of the light–dark-cycle), allowing the animal to maintain its nightly activities during winter (Kirsch *et al.* 1991, Herwig *et al.* 2007). Importantly, the use of daily torpor during winter is spontaneous and unpredictable. In controlled laboratory conditions with food and water *ad libitum* and stable moderate ambient temperatures of 18 to 21°C, some hamsters use torpor only occasionally, whereas others enter torpor five to seven times a week. Additional energetic challenges are able to influence torpor behavior in winter-adapted animals. When food is restricted, hamsters mainly increase torpor incidence (Ruf *et al.* 1993, Diedrich *et al.* 2015), colder temperatures down to 5°C will decrease body temperature during torpor to minimally 12°C, and increase incidence as well as duration (Ruf *et al.* 1993). However, when ambient temperature falls below 5°C, torpor use decreases and entirely ceases at –1°C, where the risk of unsuccessful rewarming appears to be too high (Heldmaier & Ruf 1992). When torpor is entered frequently, about 30% of energy can be saved as opposed to constant normothermia. Additionally, multiple parameters such as the degree of winter adaptation or the nocturnal locomotor

activity influence the overall energy saving capacity (Heldmaier & Ruf 1992).

Besides spontaneously occurring in winter, Djungarian hamsters can also use torpor in response to acute and severe energy deficits at any time of year. When animals have lost approximately 30% of summer body weight in response to food restriction, they will also start to enter torpor (Ruby & Zucker 1992). Fasting-induced torpor, however, differs from spontaneous daily torpor in several metabolic parameters, duration and timing (Diedrich *et al.* 2015).

Endocrine and energetic control of daily torpor

Spontaneous daily torpor only occurs when adaptations of fur, body weight and gonads are completed and it has been shown that the accompanying reductions in prolactin, leptin, growth hormone and testosterone are permissive for torpor behavior (Ruby *et al.* 1993, Freeman *et al.* 2004, Scherbarth *et al.* 2015). When these hormones are supplied, they are able to reduce torpor incidence or entirely block torpor. However, none of these hormonal changes alone is able to provoke a torpor bout and although substantial knowledge exists about endocrine and energetic prerequisites for spontaneous daily torpor in the Djungarian hamster (reviewed in Cubuk *et al.* 2016), the proximate signal that decides whether an animal enters torpor on a particular day remains unknown. In the following, we summarize the current state of knowledge about two potential regulatory factors, namely thyroid hormones and glucose, in photoperiodic adaptation as well as acute torpor regulation in *Phodopus sungorus*.

In the last decade, thyroid hormone metabolism has regained substantial attention as important regulator of seasonal adaptations. An increasing body of data suggests that the physiological, and consequently hormonal, seasonal changes are driven by local thyroid hormone availability in the hypothalamus (Barrett *et al.* 2007, Hanon *et al.* 2008, Nakao *et al.* 2008). Our own data support the idea that thyroid hormone metabolism in the hypothalamus is also directly involved in torpor control (Bank *et al.* 2017). In addition, much earlier research has provided evidence for an important influence of individual glucose availability on ultimate torpor regulation (Steinlechner *et al.* 1986, Ruf *et al.* 1991, Dark *et al.* 1999, Heldmaier *et al.* 1999). However, information on seasonal as well as circadian glucose profiles in relation to torpor behavior still remains fragmented, and should thus be readdressed focusing on proximate induction of daily torpor.

Thyroid hormones

In mammals, thyroid hormones are produced in the thyroid gland which mainly releases thyroxine (T4) and smaller amounts of tri-iodothyronine (T3) into the circulation. In the blood, the majority of thyroid hormones are bound to binding proteins like thyroxine binding globulin, transthyretin and albumin so that only a small amount of free thyroid hormones is available for transport into target tissues and cells (Yen 2001). T3 is the bioactive form of thyroid hormones that can be derived from T4 intracellularly. Whereas circulating thyroid hormone concentrations are maintained relatively stable, thyroid hormone state may substantially differ between tissues (reviewed in Little 2018). Thyroid hormones enter tissues via the monocarboxylate transporter 8 and 10, the L-type amino acid transporter 1 and 2 or the organic anion transporting peptide 1c1 (Visser *et al.* 2011). Intracellular thyroid hormone concentrations are determined by the activity of three enzymes catalyzing outer ring deiodination (deiodinase type 1 and 2) or inner ring deiodination (deiodinase type 1 and 3) and thereby activate or deactivate thyroid hormone, respectively. The active T3 is well known as a potent modulator of energy balance by regulating adaptive thermogenesis in peripheral tissues (reviewed in Silva 2006). One of its best known effects is the activation of uncoupling protein 1 that uncouples ATP synthesis in the mitochondrial membrane to generate heat. More recently, T3 has also been shown to regulate food intake and energy expenditure by central mechanisms (reviewed in Herwig *et al.* 2008). Its multiple effects on energy homeostasis make T3 an interesting candidate to adjust annual changes in energy balance and thermoregulation.

Seasonality of thyroid hormone metabolism

In the serum of Djungarian hamsters, seasonal variations in free and total T3 and T4 concentrations have been described. Free thyroid hormone concentrations were only determined in one study by Seidel *et al.* (1987). Profiles of free T3 as well as T4 matched those of total thyroid hormones, although concentrations were decreased by a factor of approximately 1000. For total plasma T3, Seidel and coworkers reported a nadir of approximately 0.6 ng/mL between June and October, followed by an increase in November, reaching a high plateau between January and April (approximately 0.9 ng/mL) under natural photoperiod but constant ambient temperatures in adult animals. In the same animals, total T4 levels

increased from lowest concentrations in October (approximately 4 µg/dL) to highest values in April (approximately 9 µg/dL) and decreased again until October (Seidel *et al.* 1987). Slightly lower total serum T3 and T4 levels were measured under laboratory conditions in artificial photoperiod (Herwig *et al.* 2009). Nevertheless, like under natural photoperiod, T3 and T4 concentrations were increased after eight weeks of short photoperiod exposure from approximately 0.3 ng/mL to 0.5 ng/mL and from approximately 1.5 µg/dL to 2.1 µg/dL, respectively. This less pronounced increase in total thyroid hormones, however, can be explained by the relatively short time the animals had spent in short photoperiod conditions, and it is likely that samples were taken before the hormones had reached their peak (Herwig *et al.* 2009).

Intriguingly, T3 concentrations in the hypothalamus appear to be regulated differently from the circulating levels. Whereas T3 concentrations are higher in the periphery under short photoperiod, expression patterns of deiodinase enzymes as well as *in vivo* studies suggest decreased T3 levels in the hypothalamus during winter (Barrett *et al.* 2007, Herwig *et al.* 2009, Murphy *et al.* 2012). Although no actual measurements of hypothalamic T3 concentrations exist, there is a substantial body of indirect evidence, that local adjustments of T3 concentrations in the hypothalamus are controlled by changing photoperiod and concomitant melatonin secretion from the pineal gland and act as central driver of seasonal adaptations in body weight and reproduction (Barrett *et al.* 2007, Hanon *et al.* 2008, Nakao *et al.* 2008, Herwig *et al.* 2009). The precise relationships and pathways between seasonal adaptations, melatonin and thyroid hormone metabolism in the hypothalamus have been a matter of very active research and reviewed in detail elsewhere (Yoshimura 2013). In brief, changing day length is translated into a hormonal signal in the pineal gland that receives photoperiodic information from the eyes and releases melatonin only during the night. The duration of melatonin secretion precisely reflects the season and affects thyroid-stimulating hormone signaling in the pars tuberalis of the pituitary gland that eventually controls deiodinase expression and thereby T3 concentrations in the hypothalamus. Also in Djungarian hamsters, hypothalamic T3 concentrations have been shown to regulate multiple aspects of seasonal physiology including long-term body weight changes and torpor expression. When T3 is chronically released into the hypothalamus from silastic implants, short photoperiod-induced body weight loss is prevented. When the implants are placed in short photoperiod-adapted animals, body weight gain

is induced until the long photoperiod body weight is reached after only three weeks (Barrett *et al.* 2007, Murphy *et al.* 2012). The mechanisms by which T3 controls this long-term shift in body weight, however, remain to be revealed.

The role of thyroid hormones in torpor expression

In Djungarian hamsters, circulating thyroid hormone concentrations increase during winter with highest levels during torpor season (Seidel *et al.* 1987). On the one hand, this makes sense because high thyroid hormone levels might contribute to the overall increased thermogenic capacity during winter allowing the animals to generate sufficient heat in the cold environment (Heldmaier & Steinlechner 1981, Seidel & Heldmaier 1982). On the other hand, high thyroid hormone concentrations might waste unnecessary energy and also hinder the expression of torpor during which heat generation needs to be inhibited. Short-term changes in circulating thyroid hormone content on a daily level might be one way to overcome this dilemma, but the limited available data do not support this hypothesis. Seidel and coworkers do not indicate whether thyroid hormone concentrations were measured in samples from torpid or non-torpid animals during winter (Seidel *et al.* 1987). However, Bank and colleagues found no differences in total serum thyroid hormone concentrations between short photoperiod-adapted torpid and non-torpid Djungarian hamsters (Bank *et al.* 2015). Hence it is likely, that the conflicting thermoregulatory demands are regulated at a subtler level. Thyroid hormones potently increase thermogenesis in brown adipose tissue but also rely on adrenergic activation via the systemic nervous system. Bräulke and colleagues could successfully abolish torpor expression for at least four days via the reversible inhibition of the sympathetic nervous system with a single 6-hydroxy-dopamine injection (Bräulke & Heldmaier 2010), suggesting that successful torpor expression depends on an overall intact sympathetic signaling that might rapidly inhibit (entrance) or disinhibit (arousal) successful thermogenesis. Constant thyroid hormone availability could ensure rapid rewarming from torpor upon activation of the sympathetic nervous system.

Nevertheless, pharmacological manipulation of the thyroid hormone system strongly affects torpor behavior demonstrating the importance of appropriate thyroid hormone metabolism in the circulation as well as the central nervous system. In line with the potent peripheral thermogenic effect of T3, we could show in

the laboratory that systemic reduction of T4 and T3 by methimazole treatment via drinking water increased torpor incidence, duration and depth (Fig. 2A), whereas systemic application of T3 in short photoperiod-adapted hamsters blocked torpor behavior (Fig. 2C). It is likely that these effects are at least partly mediated by peripheral thermogenic mechanisms, since methimazole treatment caused a significant reduction of *Uncoupling protein 1* gene expression in the brown adipose tissue of torpid animals (Bank *et al.* 2015). Interestingly, only the active T3, but not the precursor T4 affected torpor behavior (Fig. 2B). In this study, only body temperature was assessed to record and analyze torpor. Measurements of metabolic rate, the major source of heat generation in endothermic mammals, would allow a more precise characterization of thyroid hormone effects on torpor. This is of special importance since Bräulke and colleagues showed that application of the naturally occurring thyroxine derivative 3-iodothyronamine led to a rather counterintuitive drop in metabolic rate as well as a switch from carbohydrate- to lipid-based metabolism in short photoperiod-adapted hamsters without significant influence on body temperature (Bräulke *et al.* 2008).

Given its central role in long-term body weight control as well as integration of short-term energetic challenges, it can be assumed that tissue specific T3 action in the hypothalamus is also involved in torpor control (Herwig *et al.* 2009). To date, two studies have shown that hypothalamic T3 administration is able to block torpor (Murphy *et al.* 2012, Bank *et al.* 2017). In the approach by Murphy and colleagues, silastic implants chronically released T3 into the hypothalamus of short photoperiod-adapted hamsters, which quickly induced body weight gain. It was noted, that the animals stopped expressing torpor upon treatment, however, it remained unclear whether torpor was directly blocked by T3-mediated mechanisms in the brain, or indirectly by the increased body weight and possibly associated leptin changes (Freeman *et al.* 2004). To clarify these questions, we recently used microdialysis to acutely apply T3 to short photoperiod-adapted hamsters and torpor expression ceased within three days of application without body weight being affected (Fig. 2D), suggesting a direct T3-driven mechanism in the hypothalamus involved in torpor control (Bank *et al.* 2017). Hitherto, it is not possible to pharmacologically decrease T3 concentrations in the hypothalamus and assess whether a local reduction of T3 would be sufficient to induce a torpor bout. However, gene expression data of the T3-activating enzyme *Type 2 deiodinase* support this idea. The downregulation of

Figure 2

Body temperature recordings of short photoperiod-adapted Djungarian hamsters treated with (A) methimazole, (B) thyroxine (T4), and (C) tri-iodothyronine (T3) via drinking water or (D) T3 via intrahypothalamic microdialysis. During the first ten days, animals remained untreated to assess individual torpor behavior. The dark gray bars indicate the following treatment period. The light gray bar in D indicates the control days during which the microdialysis membrane was perfused with Ringer's solution only.

this enzyme in the hypothalamus during spontaneous daily and fasting-induced torpor suggests an important role of reduction of T3 availability in natural situations (Bank *et al.* 2015, Cubuk *et al.* 2017a). However, many other components like deiodinase enzymes, transporters and receptors are involved in T3 availability in the brain and require much more detailed analysis over the course of a torpor bout (Fig. 5).

The complex regulatory machinery involved in circulating as well as tissue-specific thyroid hormone metabolism, in the long term but also acutely, makes it difficult to disentangle the mechanisms of thyroid hormone action. The available data suggest that thyroid hormone availability to the hypothalamus is involved in both long-term preparatory and acute torpor regulation in the Djungarian hamster, but the downstream mechanisms are yet unknown.

Glucose

In Djungarian hamsters, long-term moderate food restriction can induce torpor under long photoperiod conditions but also increase torpor incidence under short photoperiod conditions (Steinlechner *et al.* 1986, Ruby & Zucker 1992, Ruf *et al.* 1993). Although physiological characteristics of fasting-induced torpor in long photoperiod-adapted animals and spontaneous daily torpor in short photoperiod-adapted animals are substantially different (Diedrich *et al.* 2015), it is reasonable to assume that long-term energy balance as well as the acute energetic state and the respective endogenous signaling are involved in torpor induction and control. One of the most important signals for a long-term seasonal adjustment of energy homeostasis is the peptide hormone leptin, which is secreted by white adipocytes, whereby the amount of fat mass is positively correlated

with the circulating leptin concentration. When leptin reaches the brain it communicates the state of internal energy stores to hypothalamic neurons; more precisely it activates anorexigenic and deactivates orexigenic neurons in the arcuate nucleus (for review see [Belgardt & Brüning 2010](#)). With regard to short photoperiod-adapted Djungarian hamsters, it could be shown that body fat mass and consequently leptin concentrations are strongly reduced to a lowered set point of energy homeostasis ([Klingenspor *et al.* 2000](#)) and moreover seem to be permissive for torpor expression ([Freeman *et al.* 2004](#)). However, when the animals have reached this set point, individual hamsters still favor different strategies to cope with the same energetic challenges. While some animals show a high and frequent torpor incidence in combination with reduced food consumption and nightly foraging, others rarely show torpor, but increase feeding and foraging ([Ruf *et al.* 1991, 1993](#)). Within this behavioral range, it is assumed that Djungarian hamsters use single torpor bouts to flexibly adjust their body homeostasis to acute energetic changes to stay in long-term energetic balance. Thus, the hamsters need an additional signal which communicates their short-term energetic state predominantly based on quickly available energy sources like glucose, namely insulin.

Reviewing the available data, we discuss glucose and insulin as potential acute regulatory signals for the expression of spontaneous daily torpor and again differentiate long-term seasonal adaptations of glucose metabolism from acute changes in glucose availability that challenge the hamsters' energy balance on a daily basis.

Seasonality of glucose metabolism

Applying general knowledge of glucose metabolism to Djungarian hamsters is difficult because many of these animals exhibit a genetically determined inappropriate hyperglycemia with high plasma glucose levels of up to approximately 250 mg/dL, as opposed to rats (160 mg/dL), mice (190 mg/dL) or humans (110 mg/dL) ([He *et al.* 2017](#)). This often results in an early onset of ketonuria and glycosuria, associated with glucose levels even higher than 300 mg/dL ([Herberg *et al.* 1980](#)). The documented blood glucose concentrations of healthy hamsters under long photoperiod conditions vary in a broad range between 70 and 250 mg/dL, although the majority of studies report mean values between 100 and 150 mg/dL ([Vesely & Herberg 1981](#), [Bartness & Clein 1994](#), [Bartness *et al.* 1995](#), [Garcia *et al.* 2010](#), [Carlton & Demas 2017](#),

[Lewis *et al.* 2017](#), [Cázares-Márquez *et al.* 2019](#)). At least to some extent, this high variability can be attributed to different gender, feeding state, sampling time point and measurement methods, which makes it impossible to report general seasonal or circadian systemic glucose profiles in this species.

Irrespective of variability, the overall elevated glucose levels in Djungarian hamsters resemble early symptoms of diabetes mellitus and are accompanied with a peripheral insulin insensitivity ([Herberg *et al.* 1980](#)). This apparently pathologic condition with high blood glucose levels as well as body and fat mass characterizes the physiology of long photoperiod-adapted hamsters ([Tian *et al.* 2017](#)). Interestingly, Bartness and Clein observed that neither a naturally (insulin) nor an artificially (2-deoxy-D-glucose) induced reduction in glucose availability were able to modulate food hoarding or food intake after an acute phase of food deprivation ([Bartness & Clein 1994](#)). This implies that in long photoperiod-adapted hamsters, the energetic state to induce an energy demanding behavior like food hoarding is not compromised by the current blood glucose level.

Despite the extreme adaptations to short photoperiod that change the obese and diabetic-like phenotype of Djungarian hamsters into a lean phenotype, there is no clear picture on seasonal changes of blood glucose levels. While early measurements showed a significant reduction of blood glucose from approximately 130 mg/dL in long photoperiod to 80 mg/dL in short photoperiod ([Bartness *et al.* 1995](#)), these results could not be confirmed in later studies and again, glucose values varied between 100 and 250 mg/dL after at least 12 weeks of short photoperiod adaptation ([Garcia *et al.* 2010](#), [Samms *et al.* 2015](#), [Cázares-Márquez *et al.* 2019](#)). In contrast, blood insulin levels have consistently been shown to decrease from approximately 5 ng/mL in long photoperiod conditions to 1 to 2 ng/mL in short photoperiod conditions ([Korhonen *et al.* 2008](#), [Cázares-Márquez *et al.* 2019](#)). Tups and colleagues could additionally demonstrate a substantial downregulation of the insulin receptor in the hypothalamus of juvenile hamsters that had been exposed to short photoperiod for eight weeks ([Tups *et al.* 2006](#)). Since short photoperiod exposure induces a voluntary reduction in food intake and body weight, it seems to be counterintuitive to downregulate insulin signaling which has been shown to exhibit central anorexigenic effects comparable to those of leptin. However, as insulin treatment of diabetic hamsters did not interfere with their short photoperiod adaptation, insulin signaling and presumably blood glucose seem to play a minor role in the long-term seasonal regulation of

energy intake and expenditure of Djungarian hamsters (Bartness *et al.* 1991).

Several studies have provided evidence for a synergistic action of leptin and insulin in the regulation of energy balance, since orexigenic and anorexigenic neurons of the arcuate nucleus which control energy intake and expenditure express receptors for leptin as well as insulin. Both hormones exhibit catabolic effects, presumably at the level downstream of their respective receptors (Niswender *et al.* 2004). In line with this hypothesis, the reduction of insulin signaling during short photoperiod was proposed to depend on the overall reduction of body fat stores, mediated by an enhanced central leptin sensitivity, overriding the insulin signal to prevent a catabolic overdrive (Tups *et al.* 2006, Korhonen *et al.* 2008). To maintain an adequate central insulin-mediated responsiveness to changing glucose concentrations, downregulation of the *Protein tyrosine phosphatase 1B* gene expression in the hypothalamus might serve as indirect solution to increase both central insulin sensitivity and insulin leptin cross-talk efficiency (Elchebly *et al.* 1999, Asante-Appiah & Kennedy 2003). Moreover, fibroblast growth factor signaling, another regulator of glucose homeostasis, is altered under short photoperiod exposure. Inhibition of the fibroblast growth factor receptor 1c via central treatment suppressed appetite, decreased insulin and increased energy expenditure in long photoperiod-exposed hamsters, while comparable effects on insulin and glucose could not be found under short photoperiod conditions (Samms *et al.* 2015).

Taken together, studies on glucose metabolism in Djungarian hamsters do not provide evidence for its involvement in long-term adaptations of energy balance on a seasonal scale. Nevertheless, short photoperiod exposure is accompanied with readjusted glucose as well as insulin signaling in the brain, which does not rule out the possibility of glucose as a fast and flexible regulatory signal for the short-term adjustments of energy balance on a daily base, that is, the expression of spontaneous daily torpor.

The role of glucose in torpor expression

Although the role of glucose in spontaneous daily torpor expression of Djungarian hamsters has been a constant subject of studies over the last twenty years, only few and contradictory results have been published. In 1999, Dark and colleagues measured 28% lower blood glucose levels in hamsters entering torpor (65 mg/dL, body temperature=31°C) compared to normothermic hamsters (90 mg/dL, body temperature=37°C) (Dark *et al.* 1999).

Only two months later, another study described high blood glucose levels (108.6 ± 4 mg/dL) during the first hours of a torpor bout and significantly lower values of 78.6 ± 6 mg/dL only two hours after a body temperature decrease below 32°C (Heldmaier *et al.* 1999). This was in accordance with the animals' respiratory exchange rate (RER), showing that torpor is entered from a state of glucose metabolism (RER approximately 1.0) and shifts to lipid metabolism (RER approximately 0.7) toward the end of the torpor bout (Heldmaier *et al.* 1999, Diedrich *et al.* 2015).

Hence, it remains unclear whether the reduction of blood glucose levels is the cause for or the consequence of spontaneous daily torpor entrance. One of the biggest drawbacks of the described experiments is that blood samples could only be taken punctually and *post mortem*. These measurements do neither allow assessment of glucose state just prior to torpor entrance (which is unpredictable until metabolic rate and body temperature eventually drop), nor do they permit repeated sampling in the same animal. Due to the hamsters' small size and blood volume, continuous blood glucose measurements were not possible at the time. Therefore, the question was approached by manipulating glucose homeostasis to either investigate its influence on torpor in short photoperiod-adapted hamsters or to investigate whether reduced glucose availability alone is sufficient to induce torpor in long photoperiod-adapted hamsters.

Reduction of glucose by diet

The impact of acute energy availability on torpor expression in Djungarian hamsters was described in the late eighties and early nineties. While Steinlechner and colleagues were able to provoke fasting-induced torpor via moderate long-term food restriction in long photoperiod-adapted hamsters, Ruf and colleagues could demonstrate that individual spontaneous daily torpor incidence decreased with a high caloric cafeteria diet, whereas food restriction increased torpor incidence in short photoperiod-adapted hamsters (Steinlechner *et al.* 1986, Ruf *et al.* 1991). Although the latter study did not directly examine the impact of reduced glucose availability, it could show that a carbohydrate-rich wheat diet had no effect on torpor incidence (Ruf *et al.* 1991). Both studies observed several differences between fasting-induced torpor and spontaneous daily torpor that were characterized in detail only recently. The two forms of torpor differed in preconditioning but also timing as well as general appearance of individual bouts (reviewed in Diedrich *et al.* 2015) (Fig. 3A). Fasting-induced torpor

bouts of hamsters in long photoperiod were shorter and shallower while arousal took longer when compared to spontaneous daily torpor bouts of hamsters in short photoperiod (Diedrich *et al.* 2015). Moreover, fasting-induced torpor bouts were entered from a metabolic state of energy deficit as indicated by a very low RER of 0.65 that is measured during lipid oxidation. In contrast, spontaneous daily torpor entrance occurred at RER values of 0.85, representing the usual glucose-dominated energy metabolism during the hamsters' resting phase (Heldmaier *et al.* 1999, Diedrich *et al.* 2015). Food restriction in short photoperiod increased torpor incidence, but the characteristics of spontaneous daily torpor bouts were maintained. These differences describe fasting-induced torpor and spontaneous daily torpor as two distinct forms that are used as emergency shutdown under acute energy challenges and as a flexible mechanism integrated in the overall energy saving phenotype of short photoperiod-adapted hamsters, respectively (Diedrich *et al.* 2015).

Figure 3
Body temperature recordings of Djungarian hamsters in (A) hypothermia resulting from natural metabolic downregulation during fasting-induced and spontaneous daily torpor (own data) in comparison to (B) artificial hypothermia after metabolic depression via treatment with 2-deoxy-D-glucose (2-DG, data from Dark *et al.* 1994).

Reduction of glucose by 2-deoxy-D-glucose and insulin

Although food hoarding and intake have been investigated in response to a carbohydrate-reduced diet, no attention has been paid to torpor behavior during dietary reduction of glucose (Wood & Bartness 1996). Alternatively, glucose availability was reduced pharmacologically and the effect on torpor expression was examined in several studies.

In 1994, it was first reported that the injection of the competitive glucose analog 2-deoxy-D-glucose (2-DG) with dosages from 1.5 to 2.5 mg/kg body weight resulted in a reversible reduction in body temperature below 30°C in 79% of long photoperiod-adapted hamsters within 50 minutes (Dark *et al.* 1994). As this body temperature reduction met the criteria routinely used for torpor definition, the authors hypothesized that the 2-DG-induced reduction in glucose availability might serve as the proximate signal of torpor induction. These results were confirmed in the following years, but several differences in energy and hormone state were identified between the 2-DG-induced hypothermia, fasting-induced torpor and spontaneous daily torpor (Dark *et al.* 1996, Stamper *et al.* 1998) (Fig. 3B). Unfortunately, no metabolic rate profiles, RER or blood glucose levels were assessed. Stamper and colleagues further reported a decreased incidence of 2-DG-induced hypothermia in short photoperiod-adapted hamsters that had already shown spontaneous daily torpor prior to injection (1999). From these puzzling results, it was concluded that glucoprivation does not proximately induce torpor by an increased responsiveness to glucose availability and that torpor expression might be unrelated to concurrent metabolic fuel availability (Stamper *et al.* 1999). This assumption is supported by data showing that insulin injections, inducing hypoglycemia in a more physiological range, do not result in torpor-like states (Dark *et al.* 1999).

In summary, various attempts to manipulate glucose availability were not able to clarify the potential role of glucose regulation of spontaneous daily torpor. Moreover, it is unknown to which extent the glucose concentration in the circulation of hamsters that are about to enter a torpor bout is mirrored in the brain and how the hypothalamus as potential regulatory center of torpor expression receives this metabolic information. Ongoing developments in glucose telemetry and microdialysis (Lo Martire *et al.* 2018) that allow continuous and *in vivo* central and peripheral measurements of glucose levels of Djungarian hamsters combined with detailed analysis of metabolic rate and body temperature are very promising methods to contribute to a better understanding of the energy use and requirement of spontaneous daily torpor in Djungarian hamsters.

Central integration of signals modulating daily torpor expression

In the Djungarian hamster, the expression of torpor behavior is dependent on the signaling of various peripheral hormonal systems changing with seasons as well as circadian timing mechanisms and nutritional state that may overrule the seasonal hormonal signals if necessary. This complex cocktail requires the brain for integration and orchestration to eventually regulate metabolic output. The hypothalamus is the part of the brain that regulates energy homeostasis and has been shown to be involved in the regulation of short-term energetic challenge that is, food restriction or fasting, as well as long-term changes in body weight set point in a seasonal setting (Abizaid *et al.* 2006, Morgan *et al.* 2006). With its complex organization including specialized cell types, multiple nuclei and pathways, the hypothalamus is able to sense and integrate hormonal and metabolic factors from the periphery as well as time cues from the environment to control food intake and metabolism, hormonal systems and body temperature.

Neuronal influence on daily torpor expression

Several hypothalamic structures have been shown to be involved in torpor regulation in Djungarian hamsters. The arcuate nucleus is essential in regulating food intake and energy expenditure. Two neuronal populations expressing neuropeptide Y and agouti-related peptide or proopiomelanocortin and cocaine- and amphetamine-regulated transcript drive orexigenic and anorexigenic physiological responses in mammals, respectively (Abizaid *et al.* 2006). Over seasons, only subtle gene expression changes could be found in these signaling pathways, suggesting appropriate energy balance despite the pronounced differences in body weight. Also during spontaneous daily torpor no gene expression changes were found (Cubuk *et al.* 2017a). Although no signaling pathways could be nailed down yet, it has been shown that lesions of the arcuate nucleus prevented torpor in short photoperiod-adapted Djungarian hamsters, clearly showing its participation (Pelz *et al.* 2008). Moreover, injection of the orexigenic neuropeptide Y into the hypothalamus induced a torpor-like state in hamsters under long photoperiod, that however might reflect fasting-induced torpor (Paul *et al.* 2005).

An earlier lesion experiment demonstrated the involvement of the paraventricular nucleus on torpor expression in Djungarian hamsters. However, the inhibition of torpor via bilateral ablation of this nucleus

was only successful in those short photoperiod-adapted hamsters that also showed an increase in food intake, body and fat weight, as well as testes weight (Bittman *et al.* 1991, Ruby 1995). Hence, it is likely that the paraventricular nucleus affects torpor behavior indirectly by regulating the short photoperiod-induced set points of reduced food intake, body weight and reproductive state which are permissive for torpor expression (Cubuk *et al.* 2016).

The precise circadian control of short spontaneous daily torpor expression in Djungarian hamsters implicates a role for the suprachiasmatic nucleus - the master circadian clock and main driver of all endogenous rhythms - in torpor regulation. Lesions of the suprachiasmatic nucleus in Djungarian hamsters resulted in a rapid restoration of a long photoperiod-phenotype with increased food intake, body composition as well as reproductive state and led to a pronounced inhibition of torpor expression. Interestingly, torpor could be reinstated via food restriction, but with a disrupted circadian rhythmicity (Ruby *et al.* 1989, Bittman *et al.* 1991, Kirsch *et al.* 1991, Ruby & Zucker 1992). The authors reported that their respective surgeries often destroyed other hypothalamic nuclei like the arcuate nucleus and the ventro- or dorsomedial nucleus.

We have recently screened the hypothalamus by Illumina sequencing for differentially regulated genes during entrance into torpor to identify potentially novel mechanisms of its proximate induction. The genes identified, however, appear to be rather involved in general adaptive and or protective processes during torpor than in specific metabolic signaling (Cubuk *et al.* 2017b). All these findings imply that the complex regulation of torpor is likely to be regulated by several hypothalamic structures and a more precise anatomical characterization of the participating nuclei in torpor regulation is urgently needed.

Unfortunately, little information is available on the participation and thus activation of brain areas during torpor. Only one study has investigated which hypothalamic nuclei might be activated during metabolic depression in Djungarian hamsters by analyzing protein expression of the immediate early gene *c-fos*. This study however was conducted during 2-DG-induced hypothermia of long photoperiod-adapted hamsters, a situation that is unlikely to reflect spontaneous daily torpor (Park & Dark 2007). The only two other available studies show *C-fos* gene and C-FOS protein expression over the course of a deep hibernation bout in thirteen-lined ground squirrels (Bratincsak *et al.* 2007) and arctic ground squirrels (Ikeno *et al.* 2017), respectively. In both studies,

the suprachiasmatic nuclei were activated predominantly during early arousal, but Bratincsak and colleagues could additionally show a strong transcriptional activation in the non-neuronal tanycytes during late torpor and early arousal (Bratincsak *et al.* 2007).

Tanycyte influence on torpor expression

Precisely orchestrated neuronal activation might only be one part of the central regulatory machinery. Glial cells largely impact on neuronal signaling and there is increasing evidence that tanycytes are crucial for signaling seasonal as well as metabolic information to the brain.

Tanycytes are glial cells located in the ependymal layer of the third ventricle of the brain, where their cell bodies are in direct contact with the cerebrospinal fluid. In the dorsal part of the third ventricle, tanycytes are referred to as $\alpha 1$ and $\alpha 2$ tanycytes that send their long processes to the ventromedial hypothalamic nucleus and the arcuate nucleus, respectively (Rodríguez *et al.* 2005). Thus, they are considered as an important interface between the cerebrospinal fluid and hypothalamic core areas that control energy balance (Langlet 2014) and direct tanycyte-neuron-contact has at least been proven for agouti-related protein and neuropeptide Y neurons (Coppola *et al.* 2007). In the ventral part of the hypothalamus, $\beta 1$ and $\beta 2$ tanycytes project to the median eminence and form a part of the blood–brain barrier via fenestrated capillaries (Rodríguez *et al.* 2005).

In contrast to hypothalamic neurons, tanycytes show pronounced morphological as well as gene expression changes in response to changing photoperiod and therefore are suggested to be key players in regulating the long-term adaptive physiological changes of Djungarian hamsters (Lewis & Ebling 2017). Tanycytes have been shown to be involved in thyroid hormone as well as glucose metabolism predestining them for torpor regulation.

Kameda and coworkers showed a pronounced reduction in tanycyte process density and plasticity during short photoperiod adaptation in Djungarian hamsters (Kameda *et al.* 2003). These morphological changes were later confirmed by Bolborea and colleagues and considered to play an important role in the melatonin-mediated changes in neuronal hormone release (Bolborea *et al.* 2011). In addition, several studies have revealed multiple differences in tanycyte gene expression profiles in response to photoperiod changes in Djungarian hamsters (Barrett *et al.* 2006b, 2007, Nilaweera *et al.* 2011) (Fig. 4).

Thyroid hormone system

Tanycytes express the cellular machinery of T3 metabolism in a season-dependent manner and thereby modulate the thyroid signaling to the hypothalamus. In response to short photoperiod, a net reduction of hypothalamic T3 concentration in Djungarian hamsters is achieved by reduced expression of the genes encoding *Type 2 deiodinase* and *Thyroid-stimulating hormone receptor* as well as an increased *Type 3 deiodinase* and *Monocarboxylate transporter 8* gene expression in the tanycytes (Barrett *et al.* 2007, Herwig *et al.* 2009, 2013). The described gene expression profile precedes the short photoperiod-induced reduction of body weight and likely the torpor-permissive thyroid hormone milieu in the hypothalamus. In torpid hamsters, *Type 2 deiodinase* gene expression decreased compared to non-torpid hamsters (Bank *et al.* 2015). Although it is not clear whether the decreased gene expression is a result of the metabolic depression or whether a further reduction in *Type 2 deiodinase* mRNA is required for successful torpor expression, these results suggest not only a long-term seasonal, but also an acute torpor-influencing effect of central thyroid hormones. The data on long-term seasonal changes in thyroid hormone metabolism suggest that hypothalamic thyroid hormone concentrations are controlled distinctly and not necessarily associated with serum thyroid hormone changes (Herwig *et al.* 2009). This differential regulation is most likely mediated by tanycytes and its physiological consequences are yet to uncover.

Glucose-sensing system

Tanycytes detect and rapidly respond to changing metabolite concentrations in the cerebrospinal fluid and regulate their transport into the hypothalamus (Travaglio & Ebling 2019). Several lines of evidence point to a role for tanycytes in glucose sensing as well as the regulation of central glucose metabolism, hence relaying important information about acute energetic state. Genes involved in glycogen and glucose metabolism have been shown to be upregulated in short photoperiod-adapted Djungarian hamsters, for example, *Phosphofructokinase C*, *Glycogen phosphorylase*, *Acetyl CoA carboxylase 1* or *Lactate dehydrogenase B* (Nilaweera *et al.* 2011, Herwig *et al.* 2012). These observations suggest that tanycytes are able to modulate metabolic fuel supply to surrounding neurons via glycogen mobilization, regulated by alternating amounts of available glucose they sense in cerebrospinal fluid and blood (Nilaweera *et al.* 2011). Furthermore, Hand and coworkers showed an increased expression of thioredoxin-interacting protein, a protein which regulates cellular

Figure 4

Immunofluorescence staining against the intermediate filament vimentin to visualize tanyocytes in the mediobasal hypothalamus of a long and a short photoperiod-adapted Djungarian hamster, scale bar 200 μ m (A). DMN, dorsomedial nucleus; VMN, ventromedial nucleus; ARC, arcuate nucleus; ME, median eminence. Summary of seasonal mRNA expression profiles over 14 weeks in short photoperiod-adapted Djungarian hamsters, where focus lies on genes related to (B) tanyocyte morphology, (C) thyroid system and (D) glucose system. *Ncam*, neural cell adhesion molecule, *Mct8*, monocarboxylate transporter 8, *Dio2*, type 2 deiodinase, *Dio3*, type 3 deiodinase, *Pfk c*, phosphofructose kinase c, *Gp*, glycogen phosphorylase, *Ldh b*, lactate dehydrogenase b, *Acc1*, acetyl-CoA carboxylase 1. Dashed lines summarize changes in independent animal groups from Barrett *et al.* (2006a), Bolborea *et al.* (2011), Kameda *et al.* (2003) (B), Barrett *et al.* (2007), Herwig *et al.* (2009, 2012) (C), Nilaweera *et al.* (2011) (D).

glucose (and lipid) metabolism, during spontaneous daily torpor in short photoperiod-adapted Djungarian hamsters (Hand *et al.* 2013). The mechanism of glucose sensing and transmission of glucose into tanyocytes in particular has not been completely revealed yet, however glucose transporter *Glut2* as well as sweet taste receptors *Tas1r2* and *Tas1r3*, which have been demonstrated to be expressed in mouse tanyocytes, are likely to be involved in their glucose sensitivity (Benford *et al.* 2017). According to two recent studies, tanyocytes in both acute brain slices and culture responded to exogenous glucose administration with large, intracellular ATP-dependent calcium waves, which further propagate through adjacent tanyocytes via an extracellular ATP diffusion and P2Y1 receptor activation (Frayling *et al.* 2011, Orellana *et al.* 2012). Apart from the above mentioned gene expression studies, no data are available on a potential seasonal adaptation of the tanyocyte glucose sensitivity, especially with regard to the fact that glucose concentrations within the rat hypothalamus are relatively stable, while glucose concentrations in the cerebrospinal fluid have been shown to change proportionally to the blood glucose concentration (reviewed in Elizondo-Vega *et al.* 2019). Again, the Djungarian hamster serves as excellent animal model to answer the questions whether tanyocyte glucose sensing is under seasonal and thus photoperiod control, whether it is involved in the regulation of food intake to seasonally adjusted set points

and whether tanyocyte processing of information on glucose availability is involved in the regulation of energy-saving mechanisms like torpor. Although many questions remain unanswered, here we provide a graphical summary of the current information about the involvement of the thyroid hormone and glucose system in torpor expression (Fig. 5).

Conclusions

Spontaneous daily torpor in Djungarian hamsters is a tightly regulated physiological process that involves a complex interplay of many preparatory and acute signals from periphery and brain. During the preparatory phase various hormonal systems are reset to a winter specific state, composing a torpor-permissive framework. Within that framework, acute factors such as energy availability may act as proximate triggers to induce a torpor bout on a particular day. However, even after decades of torpor research in Djungarian hamsters, the knowledge about potential regulatory components of for example, the thyroid hormone or glucose system remains fragmented (emphasized in Fig. 5). Although several hypothalamic nuclei have been associated with torpor behavior, it is unclear where and how peripheral and/or central signals are integrated and which pathways and mechanisms

Figure 5

Current knowledge of thyroid hormone and glucose system component profiles over the course of a spontaneous daily torpor bout in Djungarian hamsters. Respective changes are presented relative to normometabolic and normothermic profiles of the different components. *Dio2*, type 2 deiodinase mRNA expression; *Mct8*, monocarboxylate transporter 8 mRNA expression; *Trh*, thyroid-releasing hormone mRNA expression; tT3, total tri-iodothyronine; tT4, total thyroxine; *Txnip*, thioredoxin-interacting protein mRNA expression; GP, glycogen phosphorylase; GK, glucokinase; GS, glycogen synthase; RER, respiratory exchange rate; act., enzyme activity. Data summarized from Heldmaier *et al.* (1999), Hand *et al.* (2013), Bank *et al.* (2015, 2017), Diedrich *et al.* (2015).

they engage. *In vivo* techniques that allow continuous measurements of metabolic rate and biochemical endogenous parameters combined with neuroanatomical, transcriptomic and proteomic methods will be essential to disentangle the complicated networks involved in regulation of the fascinating phenomenon torpor. The sum of findings has great potential to help optimizing conditions in human surgeries and traumatic events, and might one day facilitate interstellar travels.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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Author contribution statement

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