REVIEW

Endocrine mechanisms of seasonal adaptation in small mammals: from early results to present understanding

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Abstract Seasonal adaptation is widespread among mammals of temperate and polar latitudes. The changes in physiology, morphology and behaviour are controlled by the photoneuroendocrine system that, as a first step, translates day lengths into a hormonal signal (melatonin). Decoding of the humoral melatonin signal, i.e. responses on the cellular level to slight alterations in signal duration, represents the prerequisite for appropriate timing of winter acclimatization in photoperiodic animals. Corresponding to the diversity of affected traits, several hormone systems are involved in the regulation downstream of the neural integration of photoperiodic time measurement. Results from recent studies provide new insights into seasonal control of reproduction and energy balance. Most intriguingly, the availability of thyroid hormone within hypothalamic key regions, which is a crucial determinant of seasonal transitions, appears to be regulated by hormone secretion from the pars tuberalis of the pituitary gland. This proposed neuroendocrine pathway contradicts the common view of the pituitary as a gland that acts downstream of the hypothalamus. In the present overview of (neuro)endocrine mechanisms underlying seasonal acclimatization, we are focusing on the dwarf hamster *Phodopus sungorus* (long-day breeder) that is known for large amplitudes in seasonal changes. However, important findings in other mammalian species such as Syrian hamsters and sheep (short-day breeder) are considered as well.

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Introduction

Habitats of polar and temperate latitudes are characterized by pronounced annual changes in environmental conditions such as day length and ambient temperature (T_a). Accordingly, vegetation and, thereby, food availability vary considerably in the course of the year. Food resources become scarce during the winter months when energy demands of endotherms are particularly high because of low T_as. Extensive acclimatization enables animals to cope with the unfavourable environmental conditions. Physiological and morphological changes, however, may take several weeks or even months. Thus, adaptations have to be initiated well in advance of the winter, and for that the animals depend on a reliable environmental time cue that signalizes early enough the upcoming cold season. Rainfall and T_a can vary considerably from year to year and provide a suitable annual course only in view of their long-term average. In contrast, alterations in day length (photoperiod) are highly predictable, and systematic changes clearly indicate the upcoming season.

Translation of photoperiodic information into a hormonal signal (melatonin) in mammals has been reviewed in detail elsewhere (Goldman 2001; Paul et al. 2008). Synthesis and secretion of melatonin by the pineal gland are restricted to the night, resulting in a melatonin peak duration that is correlated with the night length. This humoral signal induces a wide variety of effects on the animals' physiology. One of the best-studied animal models for seasonality is the Djungarian hamster (*Phodopus sungorus*; a.k.a. Siberian hamster), which is native to the steppes of

southwestern Siberia and northeastern Kazakhstan (Ross 1998). Using the example of this rodent, the complex seasonal adaptation, including changes in morphology, physiology and behaviour ("adaptive syndrome"; Heldmaier and Lynch 1986), will be described below; the main focus, however, has been put on the different endocrine systems and mechanisms involved.

Traits of seasonal adaptation in Djungarian hamsters

In the early 1960s, the Czech scientist Dr. J. Figala brought two hamster breeding pairs from the Prague zoo to the Max-Planck-Institute of Behavioural Physiology in Erling-Andechs (Germany). Together with G. Goldau und Dr. K. Hoffmann he carried out the first studies on the annual cycle in these hamsters (Figala et al. 1973). The white coat is the most obvious trait of winter hamsters (Fig. 1). In comparison with the greyish brown summer fur, the winter coat provides improved insulating properties; even the sole of the feet is covered with dense fur. Almost in parallel to the gradual change in fur colouration, the hamsters lose up to 40% of their body mass before the winter. This fact appears to be paradoxical but reflects a strategy of overwintering beneficial for a small mammal that cannot accumulate appropriate body fat stores. Measurements of oxygen consumption revealed that the winter coat compensates for the energetic disadvantage (heat loss) of an increased surface-to-volume ratio. Accordingly, the absolute amount of food that is needed is reduced in the smaller hamster (Heldmaier and Steinlechner 1981a).

Reproductive activity in Djungarian hamsters is limited to spring and summer when males and females show a functional gametogenesis. At this time, the weight of the fully developed testes is about 800–1,000 mg (Hoffmann 1973, 1979; Scherbarth et al. 2008). Regression of the testes begins in late summer and is completed ($\sim$35–50 mg) in the early autumn (Fig. 2). Testicular involution is accompanied by dramatically reduced serum concentrations of sex hormones (Schlatt et al. 1995). Reproductive quiescence ends after long-term exposure to short days (>18 weeks) inducing photorefractoriness. This loss of responsiveness to the inhibitory short photoperiod initiates spontaneous regrowth of the testes, which is already completed at the end of March. Thus, photorefractoriness allows early breeding, which presumably contributes to maximizing reproductive outcome.

When decreasing day length equals 13.5 h of light (i.e. the critical photoperiod for winter adaptation; Hoffmann 1982), the hamsters' thermogenic capacity also changes (Rafael et al. 1985a). On the one hand, the efficiency of heat generation increases even if T_a is still moderate. On the other hand, maximum capacity in non-shivering

Fig. 1 Djungarian hamster (*Phodopus sungorus*) with dark-coloured summer coat (*top*) and whitish winter coat (*middle*). The winter hamster exhibits an almost spherical posture and closed S-shaped eyelids (for explanation, see "Daily torpor"), which are characteristic of torpid hamsters. Dense fur even covers the sole of foot in this species (*bottom*)

thermogenesis (NST) only is achieved after additional cold acclimation. The increase in NST in brown adipose tissue (BAT) is due to the tenfold increase in the number of mitochondria in adipocytes (Heldmaier et al. 1981). Furthermore, the increased surface area of the small but numerous fat vacuoles (multilocular fat) compared with unilocular white fat cells might facilitate the access for lipolytic enzymes. Here, it is worth adding that the thermogenic capacity of BAT increases, even though its mass decreases in response to cold exposure and short photoperiod (Rafael et al. 1985a, b). Exceptional heat production in brown fat is linked to the uncoupling protein 1 (UCP1) located in the inner membrane of mitochondria. The
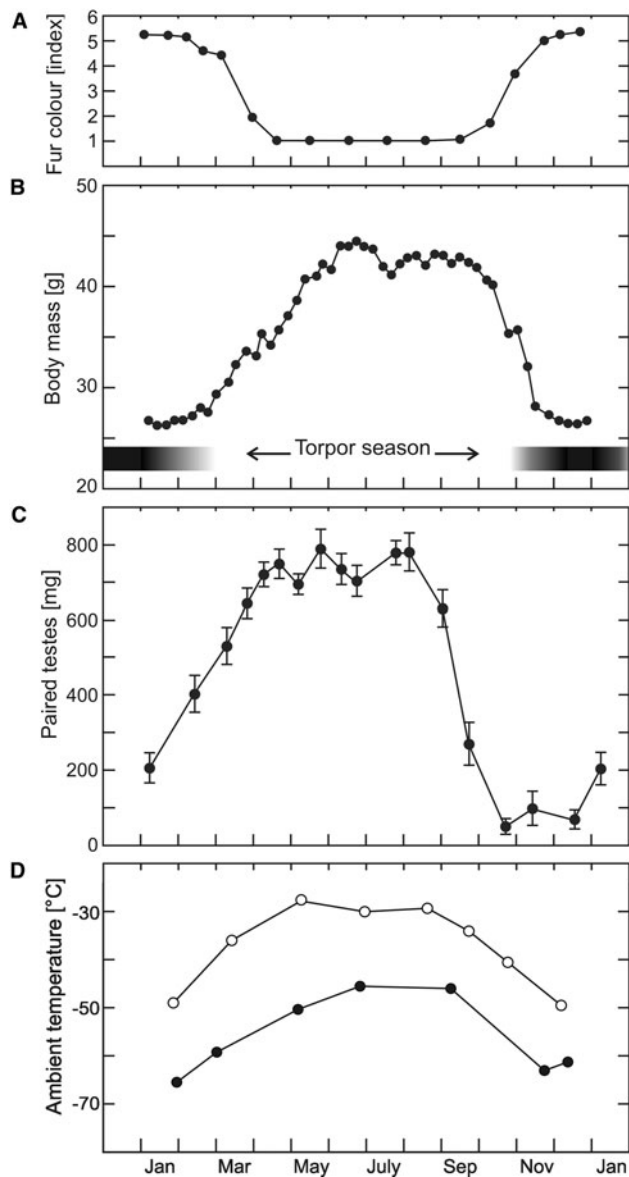
Fig. 2 Seasonal changes in **a** fur colour (*1* dark summer fur, *6* white winter fur), **b** body mass (Heldmaier and Steinlechner 1981a), **c** paired testis weight (Hoffmann 1979), and **d** cold tolerance (Heldmaier et al. 1982) of Djungarian hamsters. Cold tolerance is depicted for hamsters kept in natural photoperiod either indoors (constant moderate ambient temperature; *open circles*) or outdoors (natural ambient temperature; *closed circles*). The time span of the torpor season is indicated by the *bar* with colour gradient (**c**)

rodents but is also under circadian control (Paul et al. 2004; Ruf et al. 1989). Subsequent to the nightly activity period, metabolism may decrease to about 20% of the euthermic resting metabolic rate. Consequently, in the morning hours, body temperature (T_b) gradually drops to values between 15 and 25°C (depending on T_a). Here it is important to mention that at low environmental temperatures, regulatory heat production inhibits the decrease of T_b below the limit of about 15°C. Torpor bouts may last up to 8 h and are terminated by spontaneous arousal i.e. independent of external stimuli. Within about half an hour, the euthermic state is recovered by both NST and shivering. Thanks to controlled hypothermia, the heterothermic hamsters may reduce 24-h energy expenditure by about 65% even though they remain active during the night (Ruf et al. 1991).

Many small mammals show annual cycles similar to those in Djungarian hamsters. However, linked to the harsh environmental conditions, seasonality in Djungarian hamsters is exceptionally pronounced. The high amplitudes of seasonal traits make these hamsters an excellent animal model for investigations on the underlying endocrine mechanisms. The photoneuroendocrine system together with its hormone melatonin represents the key player for the "adaptive syndrome" (Heldmaier and Lynch 1986). This has been shown by the finding that timed daily application of melatonin causes the change from a long-day (LD) hamster (high body weight, functional gonads, summer fur) to a short-day (SD) hamster (low body weight, non-functional gonads, winter fur). Interestingly, in Djungarian hamsters a functional melatonin 2 receptor (MT_2), which is one of the two known subtypes in mammals, is lacking (Weaver et al. 1996). Thus, the MT_1 receptor appears to be sufficient for photoperiodic responses; that this applies not only for the latter species is strongly supported by recent findings in (melatonin producing) mice with targeted disruption of MT_1, MT_2 or both subtypes (Yasuo et al. 2009). Although melatonin obviously triggers winter acclimatization, the different physiological changes are not directly driven by the melatonin signal. Instead, melatonin merely provides the permissive factor for other hormonal systems, which will be described in the following.

Pelage properties

So far the endocrine mechanisms of seasonal changes in pelage have not been described in detail in any mammalian species. The blood concentration of prolactin, however, has early been identified as a crucial factor. Surprisingly, little attention has been paid to the possibility that distinct hormones might control different fur characteristics such as hair length, density, colour and growth rate (Paul et al.

function of UCP1 is to mediate the proton influx resulting in the uncoupling of the respiratory chain from oxidative phosphorylation. Thus, oxidative energy is released as heat instead of being stored as ATP (Klingenberg and Huang 1999). This mechanism in brown fat is crucial for the arousal from shallow daily torpor, which is a hypometabolic and hypothermic state, only occurring during the winter months (Heldmaier and Steinlechner 1981b). Daily torpor is not only a strictly seasonal phenomenon in these

2007). Furthermore, regulation of moulting might differ between photoperiodic and non-photoperiodic species.

Steroid hormones are already known for a long time to affect the hair cycle. In laboratory rats and mice, castration (orchidectomy and ovariectomy) accelerates hair growth (Johnson 1958a; Smart et al. 1999). In contrast, treatment with testosterone or estradiol decelerates the growth rate. Hormones of the adrenal cortex inhibit moulting, whereas adrenalectomy accelerates the process (Johnson 1958b; Rose and Sterner 1992). Moreover, it has been demonstrated that hair growth is stimulated by thyroid hormones (Ebling and Johnson 1964; Maurel et al. 1987).

Already in 1944, Bissonette and Bailey demonstrated the photoperiodic control of moulting in the stoat (*Mustela erminea*). However, 25 years have passed before the change to the white winter coat was shown to be inducible through melatonin implants. In the 1970s, studies on other small mammals such as field voles (*Microtus agrestis*; Al-Khateeb and Johnson 1971), Djungarian hamsters (Figala et al. 1973; Hoffmann 1973) and mountain hares (*Lepus timidus*; Küderling et al. 1979) confirmed the effect of melatonin. Martinet et al. (1982) were the first who provided evidence that seasonal variations in plasma concentrations of prolactin correlate with the change in fur colour. Furthermore, they could accelerate springtime moulting in American minks (*Mustela vison*) by daily injections of prolactin (Martinet et al. 1981). Thorough studies by Duncan and Goldman (1984a, b) revealed that in Djungarian hamsters, low concentrations of both prolactin and testosterone are required for the change to white winter fur. Interestingly, for moulting to the dark summer pelage a high concentration of prolactin appears to be sufficient since castrated animals also changed their fur colour. Nonetheless, the prolactin-independent influence of testosterone on the moult to the winter pelage has also been demonstrated in Syrian hamsters (Goldman et al. 1981; Paul et al. 2007).

It is worth emphasizing that Djungarian hamsters, unlike minks or stoats (Rust 1965), do not show seasonal shedding but continuous moulting combined with seasonal changes in different hair characteristics, as has been proposed by Badura and Goldman (1992). More precisely, hair length, composition and colour seasonally alter within a process of recurrent moulting waves (Kuhlmann et al. 2003). Interestingly, hair density (hairs per hair funnel) of the winter coat was not increased in hamsters kept at moderate T_a. Nevertheless, SD exposure results in more effective insulation after several weeks, which appears to be aided by an increased rate of fur regrowth (Paul et al. 2007).

The annual cycle of prolactin secretion is driven by photoperiod and thus melatonin. In hamsters and sheep, the pars tuberalis of the adenohypophysis provides the crucial interface within the melatonin-dependent control of seasonal changes in fur. The cells expressing MT_1 receptors (Dardente et al. 2003; Klosen et al. 2002; Morgan et al. 1994) regulate the prolactin secretion of the pars distalis (Lincoln et al. 2003a). The signal from the pars tuberalis to the prolactin-producing cells of the pars distalis is supposed to be mediated by a still unidentified factor (maybe more than one) called "tuberalin" (Hazlerigg et al. 1996; Morgan 2000; Morgan and Williams 1996; Stirland et al. 2001). In sheep, two genes have recently been identified that might be critical for the intrapituitary circuit controlling seasonal prolactin release (Dupré et al. 2010). Eya3 (encoding a transcription factor) and TAC1 (encoding substance P and neurokinin A) were strongly activated by long photoperiod and were shown to act on primary pituitary cells.

In addition to the indirect effect of melatonin on changes in fur, the hormone may directly affect hair pigmentation. In cultured hair follicles, melanogenesis is inhibited by melatonin resulting in unpigmented hair (Logan and Weatherhead 1980). In vivo, however, prolactin may override this in vitro effect of melatonin on melanogenesis. Daily injections of prolactin prevented the SD-induced moult to the white pelage in Djungarian hamsters (Duncan and Goldman 1984b; Smale et al. 1990).

Body weight and seasonal adiposity

In recent years, research on body weight regulation has attracted great interest because of alarming statistics on public health and obesity in western developed nations. The understanding of the neuroendocrine mechanisms underlying satiety and appetite is expected to provide novel approaches of therapy and prevention against severe over- and underweight in humans. In this regard, animal models based on brain lesions or genetic manipulations are helpful but often have an important disadvantage: the changes in body weight usually are irreversible unlike the body fat loss and gain in animals that show a seasonal body weight cycle. In the latter, both the increase and decrease in body fat stores can be induced by suitable environmental conditions. For instance, while SD-exposed Djungarian hamsters lose body weight, switching to LD conditions is sufficient to induce the recovery of the initial weight. This reversion is inducible at each time of the gradual decrease in body weight in short photoperiods. The remarkable reduction in body weight of up to 40% is predominantly due to depletion of white adipose tissue (WAT; Bartness 1996; Gorman and Zucker 1995; Klingenspor et al. 2000; Wade and Bartness 1984). Interestingly, there is also evidence that in short photoperiod not only bone (mineral) density decreases but also the skull shrinks (Pucek 1970). These changes indicate that calcitonin and parathormone
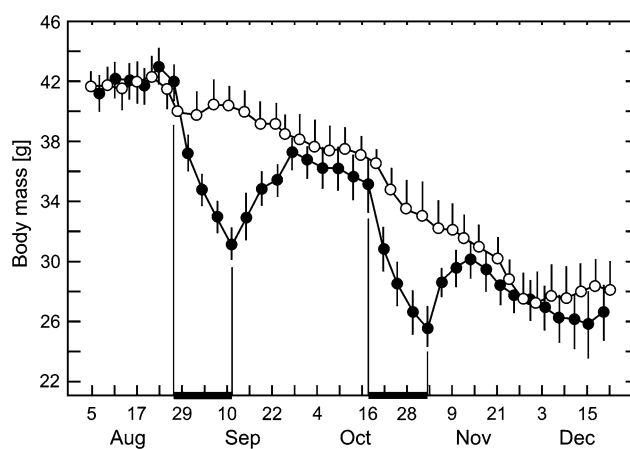
Fig. 3 Changes in body weight of Djungarian hamsters during the trajectory from high body weight in summer to low weight in winter (*open circles*). Hamsters of the second group (*closed circles*) were temporarily (*black bars*) food-restricted to 60% of ad libitum (Steinlechner et al. 1983)

might be involved; to our knowledge, however, there are no studies on this subject to date.

The continuous decrease in body weight of Djungarian hamsters is precisely regulated as has been shown in a food restriction experiment under natural lighting conditions (Steinlechner et al. 1983; Fig. 3). The findings indicate a gradual decrease in the 'body weight set-point' (sliding set-point) that is linked to the duration of SD exposure. Mercer et al. (2001) confirmed the results in hamsters kept in artificial short photoperiod. Surprisingly, it is still not clear whether the decrease in body weight is due to voluntarily reduced food intake or whether food intake decreases as a consequence of the reduction in body weight. The findings of Wade and Bartness (1984) suggested that an initial increase in energy metabolism is responsible for the decrease in body weight, which in turn causes the reduction of food intake. In contrast, examinations carried out by Knopper and Boily (2000) provided evidence that the loss of body mass is the result of a voluntarily reduced food intake.

Maintenance of energy balance relies on signals from the gastrointestinal tract and adipose tissue that reach the respective regulatory brain regions (Fig. 4). In this regard, the hypothalamus represents a key region in particular the arcuate nucleus (ARC), paraventricular nucleus (PVN), ventromedial (VMH) and dorsomedial hypothalamic nucleus (DMH) as well as the lateral hypothalamic area (LHA) (for review, see Morgan et al. 2003). The neuropeptides and neurohormones that are involved in the control of energy balance in different rodent species (for reviews, see Kalra et al. 1999; Schwartz et al. 2000) have all been found in Djungarian hamsters as well. For example, neuropeptide Y (NPY) is known to stimulate food intake (Boss-Williams and Bartness 1996), whereas the
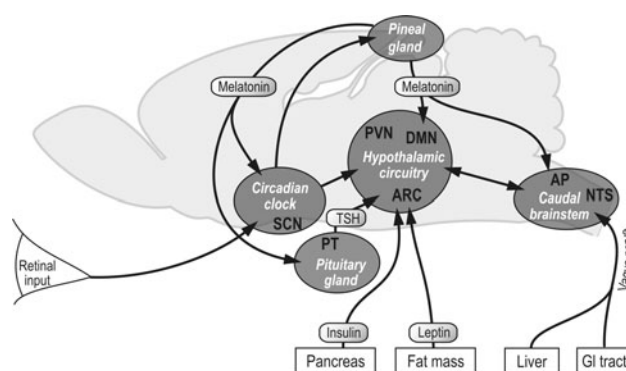

Fig. 4 Integration of humoral signals and sensory information within central circuits involved in energy balance regulation. The hypothalamic regulatory network receives information about the metabolic state (leptin, insulin) and satiety signals processed and transmitted by brainstem nuclei. Recent findings indicate that seasonal changes of *Dio2/Dio3* expression in tanycytes and thereby thyroid hormone availability in the hypothalamic regions adjacent to the third ventricle (e.g. arcuate nucleus; ARC) are controlled by the release of thyroid-stimulating hormone (TSH) from the pars tuberalis (PT) of the pituitary gland. *AP* Area postrema, *DMN* dorsomedial hypothalamic nucleus, *GI* gastrointestinal, *NTS* nucleus of the solitary tract, *PVN* paraventricular hypothalamic nucleus, *SCN* suprachiasmatic nucleus (modified after Helwig et al. 2009)

α-melanocyte stimulating hormone (α-MSH), a cleavage product of proopiomelanocortin (POMC), reduces food intake (Schuhler et al. 2003). Food restriction and low leptin concentrations increase gene expression of orexigenic peptides and, concurrently, suppress the expression of anorexigenic peptides (Mercer et al. 2000; Reddy et al. 1999; Robson et al. 2002; Rousseau et al. 2002). Hypothalamic gene expression in food-restricted (or food-deprived) hamsters, however, differs from the expression pattern in SD hamsters (Mercer et al. 2001). Despite the fact that the latter also lose weight, they are not starving but are in energetic balance (Morgan and Mercer 2001; Morgan et al. 2003). Therefore, the gradual changes in body weight and the underlying mechanism still cannot be fully explained on the basis of the known regulatory network in the hypothalamus (see also Ebling and Barrett 2008). Another important brain region, which is part of the gut-brain axis, is located in the caudal brainstem. The nucleus of the solitary tract (NTS) and the parabrachial nucleus (PBN) appear to be crucial for both processing short-term satiety signals from the gastrointestinal tract (Saleh and Cechetto 1996) and transducing of the information to the long-term hypothalamic energy balance network (Vrang et al. 2007). Recently, it has been demonstrated that the expression of some satiety-related neuropeptides (e.g. preproglucagon, cholecystokinin, glucagon-like peptide 1) and the melanocortin-4 receptor is photoperiodically regulated in the brainstem of Djungarian hamsters, indicating a photoperiod-dependent modulation of satiety signalling and, thereby, contributing to seasonal feeding behaviour

(Helwig et al. 2009). Although administration of the orexigenic peptide ghrelin has been shown to augment foraging and food hoarding, the gut-derived hormone appears not to be involved in seasonal body weight regulation (Korhonen et al. 2008; Tups et al. 2004b).

As expected, the annual photoperiod-induced changes in body weight and fat mass are closely correlated with the leptin concentration in blood (Korhonen et al. 2008). However, the fact that in fat summer hamsters the high leptin level does not evoke anorexigenic effects, unlike the gradually decreasing leptin concentration during the transition from the summer to the winter state, can only be explained with an alteration in leptin sensitivity: in the spring and summer (long photoperiod), the hamsters are virtually leptin-resistant, whereas they respond to exogenous leptin during the autumn and winter (short photoperiod) (Atcha et al. 2000; Klingenspor et al. 2000; Rousseau et al. 2002). The finding that leptin treatment at the time of the lowest body mass (in December) did not provoke a further decrease (Scherbarth et al. 2007) is well in accordance with the proposed mechanism; as the nadir is equivalent to the turning point of the body weight cycle, it is likely that the underlying mechanism had already switched to leptin resistance, which allows regaining weight. An important factor within the signalling pathway of the leptin receptor (OB-Rb), the suppressor of cytokine signalling 3 (SOCS3), appears to play a crucial role in the control of leptin sensitivity (Howard et al. 2004; Król et al. 2007; Tups et al. 2004a, b, 2006; for review, see Tups 2009). In the ARC, the leptin signalling inhibitor SOCS3 is already reduced after 4 days in short photoperiod, which results in increased leptin sensitivity previous to the decline in body weight (Tups et al. 2004a). Anorexigenic effects and increased energy expenditure due to leptin action lead to a reduction in body weight until energy balance is re-established (Tups et al. 2006). Interestingly, a remarkable difference was found in the photoperiod-dependent gene expression of SOCS3 between field voles (Król et al. 2007) and Djungarian hamsters. After the transfer from short to long photoperiod, the increase in the SOCS3 level is similar in the two species. However, in hamsters, the elevated SOCS3 level is chronically maintained under LD conditions, whereas field voles exhibit a drop in SOCS3 gene expression back to the SD level after few weeks. Since field voles maintain the high body weight in long photoperiod despite the decrease in SOCS3, leptin resistance appears to be induced by SOCS3 but, apparently, is maintained through a different mechanism downstream. Another interesting question that remains to be elucidated is how switching from leptin resistance to sensitivity (and vice versa) is triggered. Seasonal changes in circulating prolactin have been considered a possible signal (Tups 2009). This assumption is supported by evidence based on

experiments in hypophysectomized juvenile Djungarian hamsters exposed to LD (Niklowitz and Hoffmann 1988). Removal of the pituitary gland resulted not only in a change to winter fur and involution of the testes but also in cessation of growth and a slight loss of body weight. Prolactin substitution abolished the inhibitory effects of hypophysectomy on fur colour and body weight, suggesting that the pituitary hormone is involved in annual changes in body weight. The idea gets further support from the finding that pharmacological suppression of prolactin release was accompanied by a decrease in body weight in pinealectomized hamsters (Badura and Goldman 1992). Moreover, there is substantial evidence that prolactin/placental lactogen is critical for pregnancy-induced hyperphagia and leptin resistance in rats (Naef and Woodside 2007; for review, see Ladyman et al. 2010).

It seems likely that brain regions that exhibit melatonin receptors mediate the photoperiodic effects on body weight. However, from studies on sheep and hamsters (Lincoln and Clarke 1994; Lincoln et al. 2003b), we can conclude that the mechanism underlying the seasonal prolactin secretion (see "Pelage properties") is very unlikely to be a possibility for the regulation of the body weight cycle, although seasonal changes in prolactin secretion might be contributing to changes in body weight (see above). Within the hypothalamus, melatonin receptors have been localized in the suprachiasmatic nucleus (SCN), DMN, anterior hypothalamic area (AHA) and stria medullaris (Morgan et al. 1994). Lesion experiments revealed that the SCN presumably is an important interface in the photoperiodic control of body weight. Although melatonin was administered to mimic SD conditions, pinealectomized hamsters bearing SCN lesions failed to lose weight (Bartness et al. 1991).

A sympathetic efferent pathway between MT_1 receptor-expressing SCN neurons and the inguinal fat pad has been demonstrated by retrograde pseudorabies virus staining (Song and Bartness 2001). Similarly double-stained neurons were located also in other hypothalamic regions such as AHA, DMN, LHA and ARC, which all are involved in the regulation of energy balance. Based on their findings, Song and Bartness (2001) hypothesized that (1) melatonin, as neuroendocrine signal for day length, binds to neurons of the SCN and other hypothalamic areas, (2) these neurons are the origin for sympathetic innervation of WAT, (3) as a result, the photoperiodic information arrives at adipocytes, (4) increased sympathetic drive triggers lipid mobilization and (5) the size and number of adipocytes decrease (Bartness 1996; Bartness et al. 1991; Song and Bartness 2001; Youngstrom and Bartness 1998). Meanwhile, sympathetic and sensory innervations of WAT have been described in more detail (Stanley et al. 2010; for review, see Bartness et al. 2010), but their function within the

regulation of fat mass and body weight is still poorly understood.

The ecophysiological relevance of the seasonal body weight cycle still remains to be elucidated for some species. In hibernators, big mammals and migratory birds, the fat pads accumulated in the late summer and autumn serve as energy reserves (Bairlein 2002; Körtner and Heldmaier 1995; Mitchell et al. 1976; Zucker and Boshes 1982). It is also known that in small mammals (<0.1 kg), the fat stores can only be limited in size, which would be inadequate for mammals that are active during the winter. Because of the high energy metabolism at low T_a, the fat reserves would be depleted within a few days (Heldmaier 1989). Furthermore, as is mentioned above, a smaller animal, i.e. with reduced body mass (and improved thermal insulation), needs less food (Heldmaier and Steinlechner 1981a). Thus, the question arises as to what is the purpose for accumulating body fat in spring, or in other words, why do Djungarian hamsters become leptin-insensitive? 'High energy demands of reproduction' appears to be the most obvious answer. Indeed, the importance of fat stores for reproductive outcome is reflected by increased maternal investment in leptin-treated Djungarian hamsters (French et al. 2009). Additionally, a positive correlation between maternal weight and litter size, reproductive output and litter growth was found in Djungarian hamsters (Weiner 1987) and deer mice (*Peromyscus maniculatus*; Myers and Master 1983). On the other hand, male Djungarian hamsters of breeding pairs did not show a decrease in body weight (unpublished), and it is not known whether in free-living males, energetic burden during the reproductive season is comparable to those found in captive females. Moreover, the hamsters start to reduce body weight in late summer (Scherbarth et al. 2007, 2008) prior to cessation of the breeding season, just at the time when food availability (seeds, insects) is at its peak. Hence, the answer might also be linked to additional, less well understood functions of WAT. In addition to the 'conventional' role as energy store that provides fatty acids, WAT is involved in glucose homeostasis and endocrine mechanisms. For example, the most important hormone for regulation of energy balance, leptin, is mainly released by WAT. Several other proteins have been identified as endocrine or paracrine factors secreted from WAT, such as steroids, angiotensinogen, TNFα, interleukin-6, TGFβ, adipsin, and resistin (for an overview, see Trayhurn 2005; Trayhurn and Bing 2006). However, the physiological function of several of those proteins is still largely unknown. Another function of adipose tissue is to store molecules such as liposoluble vitamins. It is conceivable, therefore, that the gradual decrease in fat mass leads to a chronic release of essential nutrients that become scarce during autumn and winter.

Daily torpor

Seasonal torpor in Djungarian hamsters is dependent neither on cold load nor on food scarcity. Instead, the animals display spontaneous torpor at moderate T_a and despite food abundance. However, the first torpor bout usually occurs only after about 12 weeks of SD exposure, when the gonads are regressed and the body weight approximates its nadir (Scherbarth et al. 2008). Similarly, deer mice that displayed torpor in SD and at cold T_a exhibited atrophic testes and weighed less than animals also with atrophic testes but not showing torpor (Blank et al. 1988). A causal relation between testis regression and the display of torpor was shown in castrated hamsters in which exogenous testosterone almost completely inhibited the incidence of controlled hypothermia (Bartness et al. 1989; Vitale et al. 1985). According to the permissive role of low testosterone concentrations, the torpor season under natural photoperiod is limited to a couple of weeks (Fig. 2) and ceases when photorefractory hamsters regain body and gonadal weight. As already mentioned earlier, the SD-mediated loss of body mass is, in large part, due to degradation of stored fat. It is commonly assumed that the occurrence of seasonal daily torpor is linked to low body and fat mass, which is supported by findings that strongly suggest low leptin concentrations to be a permissive factor (Freeman et al. 2004; Korhonen et al. 2008). Studies on mice revealed not only that low leptin levels are a prerequisite for fasting-induced torpor as well, but also that both arousal from the hypothermic state as well as torpor induction need β3-adrenoceptor stimulation (Swoap et al. 2006; Swoap and Weinshenker 2008). Furthermore, the results provided evidence that noradrenergic signalling contributed to the early drop in circulating leptin during the fast, which is consistent with earlier findings, demonstrating that β3-adrenoceptor signalling in adipose tissue down-regulates leptin gene expression and synthesis (Trayhurn et al. 1995). The important role of intact noradrenergic signalling of the sympathetic nervous system was confirmed in Djungarian hamsters, in which temporary damage of catecholaminergic neurons prevented daily torpor (Braulke and Heldmaier 2010). This is surprising insofar as torpor entry is characterized by decreasing heart and respiratory rates before T_b declines (Elvert and Heldmaier 2005; Morhardt 1970), suggesting a dominant role for parasympathetic control. Remarkably, in torpid Djungarian hamsters, the typical S-shape formed by closed eyelids (Fig. 1) indicates retraction of the eyes, which may be considered as a further indication of the involvement of sympathetic nervous system.

In search of the proximate trigger for torpor entry, several substances have been demonstrated to reduce T_b. Energy metabolism has been the main focus of experiments, including administration of 2-deoxy-D-glucose

(2-DG; Dark et al. 1994), NPY (Paul et al. 2005), 5′-AMP (Swoap et al. 2007; Zhang et al. 2006), ghrelin (Gluck et al. 2006), and 3-iodothyronamine (T$_1$AM; Braulke et al. 2008). Administration of the thyroid hormone derivative T$_1$AM not only induced hypothermia but also an alteration in energy metabolism towards lipid utilization in Djungarian hamsters (Braulke et al. 2008). However, the authors stated that the properties of T$_1$AM-induced hypothermia did not resemble those of a spontaneous torpor bout, albeit torpid hamsters usually show a decrease in the respiratory quotient (Heldmaier et al. 1999), which is indicative of a shift towards fat utilization. Ghrelin treatment has been shown to deepen torpor bouts in fasted mice with intact hypothalamic ARC (non-ablated) only. Consistently, ARC ablations by monosodium glutamate in Djungarian hamsters reduced the frequency of 2-DG-induced hypothermia and prevented photoperiod-dependent torpor (Pelz et al. 2008), suggesting that the ARC plays a crucial role in torpor initiation. This is in agreement with the decrease in T_b after central application of NPY (Paul et al. 2005). Together with the inhibiting effect of leptin on hypothalamic NPY expression (Ahima et al. 1999) and the fact that NPY-expressing neurons within the ARC also express Ob-Rb receptors (Mercer et al. 1996), the findings indicate that ARC leptin/NPY-ergic signalling might play a key role in the neuroendocrine control of torpor. The physiological requirements for seasonal torpor (e.g. low leptin and testosterone concentrations), which are fulfilled only after about 12 weeks of SD acclimatization, appears likely to be also related to fatty acids. Apart from the fact that dietary fatty acids may affect the occurrence, depth and duration of torpor bouts (Geiser and Heldmaier 1995; for review, see Dark 2005), there is evidence that seasonally altered tissue fatty acid compositions allow muscles, in particular the heart, to maintain functionality during hypothermia (Geiser et al. 2007; for review, see Ruf and Arnold 2008). In fact, calcium uptake and content were found to be increased in the sarcoplasmic reticulum of ventricular myocytes of SD-acclimatized Djungarian hamsters (Dibb et al. 2005). Presumably, increased ratios between essential 6-n and 3-n polyunsaturated fatty acids (PUFA) are the crucial factor in the prevention of heart failures at low T_b. Hence, one might speculate about a connection between the SD-induced degradation of PUFA-containing fat reserves and the cellular remodelling for hypothermia.

Reproduction

Seasonal reproduction and its photoperiodic regulation have been examined more extensively than any other trait of seasonality. In the 1930s, the important role of light (photoperiod) has been described in ferrets (*Putorius*

vulgaris; today: *Mustela putorius f. furo*; Bissonette 1932) and field voles (Baker and Ranson 1932). More than 12.5 h of light per day was effective as summer-like long photoperiod, which was confirmed later for Syrian hamsters (*Mesocricetus auratus*; Elliott 1976), whereas short photoperiods (<12 h of light) represented the winter. Seasonal breeding was assumed to ensure that newborns encounter the most favourable time of the year (Baker and Ranson 1932). Indeed, factors such as T_a rain fall and food supply have a massive effect on the survival rate in offspring as the young are particularly susceptible to adverse environmental conditions (Hill 1992). Initially, however, food availability is a limiting factor in females since pregnancy and lactation represent the most energy-demanding time, especially challenging for small mammals (Bronson 1989; Speakman 2008). In animals that have a short gestation period (hamsters, voles), long photoperiods have a stimulating effect on the gonads. In contrast, short photoperiods activate the gonads of animals that have either a long gestation period (sheep) or a delayed implantation (badgers) or that exhibit hibernal latency (some bats). With regard to the influence of day length, Baker and Ranson (1932) already emphasized that they have merely described the environmental factor but not the underlying mechanism. In the 1960s, several studies showed that melatonin released by the pineal gland is involved in transmitting the photoperiodic information for gonadal responses (Czyba et al. 1964; Hoffman and Reiter 1965; Reiter and Hester 1966). Initially, short photoperiods and corresponding melatonin signals were supposed to be solely antigonadotropic, which was due to the work on Syrian hamsters (Reiter and Johnson 1974). Thorough investigations by Klaus Hoffmann revealed that the pineal gland together with its hormone melatonin may also mediate progonadotropic effects (Hoffmann 1981; Hoffmann and Kuderling 1975; Steinlechner and Niklowitz 1992; Turek et al. 1975; for review, see Turek and Campbell 1979). After the publication of the basic work on sheep (Arendt et al. 1983; Bittman et al. 1983; Lincoln 1979; Malpaux et al. 1987), the concept of melatonin encoding night lengths by signal duration (Carter and Goldman 1983a; Hoffmann et al. 1986; Reiter 1993) became established. In combination with the photoperiodic 'history', i.e. a decreasing or increasing duration of the melatonin signal, the organism obtains information on the time of the year (Goldman 2001; Hazlerigg and Wagner 2006; Paul et al. 2008; Spessert 2005).

Responses to information on season are species-dependent. In Djungarian hamsters, decreasing day lengths induce testis regression and a loss of body mass. SD-induced involution of the testes is also known for Syrian and European hamsters (*Cricetus cricetus*) but, unlike Djungarian hamsters, they increase body weight

(fat deposition for hibernation). In contrast to the antigonadotropic effect in hamsters, sheep show testicular growth in response to shortening photoperiods, and they increase body mass. It is still not known in detail how the reproductive system is affected by photoperiod and the circadian system. The duration of nightly melatonin secretion is not only pivotal for changes in fur and body weight but also for reproductive activity (Carter and Goldman 1983a, b). Different hypothalamic nuclei that express melatonin receptors are involved in activity regulation of the hypothalamic–pituitary–gonadal (HPG) axis in photoperiodic mammals. Lesions within the mediobasal hypothalamus (MBH), unlike other hypothalamic nuclei, have been demonstrated to inhibit the photoperiodic control of testis activity in Syrian hamsters (Maywood and Hastings 1995). In white-footed mice (*Peromyscus leucopus*), the use of melatonin microimplants revealed that the anterior hypothalamus is the target of antigonadal action of melatonin (Glass and Lynch 1981) and provided evidence that melatonin and testosterone act in concert to induce gonadal regression by suppressing GnRH secretion (Glass and Dolan 1988). Experiments with melatonin microimplants in the MBH of sheep revealed supporting results insofar as the secretion of gonadotropins was stimulated; the effect did not occur when implants had been placed in the AHA, LHA or pituitary gland (Lincoln and Maeda 1992a, b; Malpaux et al. 1998). Contrary to photoperiod-driven responses of the HPG axis, which take several weeks, changes in circulating prolactin are detectable already within a few days (Lincoln 1999, 2002). Therefore, 'calendar cells' have been suggested that show different temporal properties in the hypothalamus compared with the pars tuberalis (Lincoln et al. 2003b).

A breakthrough occurred with the discovery of the ligands [kisspeptins (kp)] for the G-protein coupled receptor 54 (GPR54) (Clements et al. 2001; Kotani et al. 2001). There is substantial evidence that kp, encoded by the *Kiss1* gene, act directly (via GPR54) on hypothalamic GnRH neurons. In sheep, for instance, central application of kp-10 (cleavage product) resulted in increased GnRH and pituitary LH secretion (Messager et al. 2005). Consistently, reproductively quiescent Syrian hamsters underwent testicular reactivation (in short photoperiod), including increased levels of circulating testosterone, after few weeks of i.c.v. administration of kp-10 (Revel et al. 2006). In contrast, peripheral application of kp neither prevented testicular regression nor accelerated testis recrudescence in Djungarian hamsters (Greives et al. 2008b). Although male Djungarian hamsters exhibited an increase in circulating LH in response to kp administration, FSH secretion was indicated to be unaffected. This would explain the lacking progonadal effect of exogenous kp, since elevated FSH concentrations are critical for testis

recrudescence in Djungarian hamsters (Schlatt et al. 1995). Here, it is worth mentioning that *Kiss1*/GPR54 expression in ovaries was increased after photoperiod-induced recrudescence, indicating that kp/GPR54 signalling is not only crucial for the central control of the gonadal axis but might also be involved in the regulation of ovarian function at the gonadal level in Djungarian hamsters (Shahed and Young 2009).

In rodents, *Kiss1* mRNA is predominantly expressed in the ARC and the anteroventral periventricular nucleus (AVPV) of the hypothalamus. In agreement with the putative GnRH-stimulating role of kp, *Kiss1* expression was reduced in both the ARC and the AVPV of photoinhibited male and female Syrian hamsters (Ansel et al. 2010; Revel et al. 2006, 2007). Intriguingly, in Djungarian hamsters, kp expression in SD was down-regulated only in the AVPV but increased in the ARC, and vice versa in LD (Greives et al. 2007; Mason et al. 2007). The site-dependent, opposite expression patterns of kp strongly indicate unequal roles for the ARC and the AVPV in gonadal axis regulation. This view is also supported by recent findings in Syrian hamsters (Ansel et al. 2010). The data suggest a differential regulation of *Kiss1* expression by melatonin and gonadal hormones between AVPV and ARC.

Feedback of sex steroids in photoperiodic mammals is likely to be based on changes in central hormone sensitivity (Prendergast et al. 2006), since the sex steroids' release depends on gonadal state, which in turn changes according to season. However, in male Syrian hamsters, melatonin-driven downregulation of *Kiss1* expression in the ARC is strongly suggested to be independent of testosterone feedback (Ansel et al. 2010; Revel et al. 2006). In contrast, seasonal changes in kp expression of male Djungarian hamsters appear to be regulated by photoperiod and testosterone (Greives et al. 2008a). Additionally, an impact of nutritional state on kp expression in the ARC was strikingly revealed in a 'threshold' photoperiod of 13.5 h of light (Paul et al. 2009). Indeed, leptin has earlier been demonstrated to act on *Kiss1* neurons within the ARC of leptin-deficient *ob/ob* mice (Smith et al. 2006). However, the adipose-derived hormone showed a stimulating effect on kp expression in mice, and Djungarian hamsters exhibit down-regulated *Kiss1* expression in the ARC together with high concentrations of circulating leptin (and vice versa). In this regard, seasonally changing leptin sensitivity (discussed above) might be the explanation for the reputed inconsistency. The melatonin target site(s) responsible for the control of hypothalamic *Kiss1* neurons remain(s) unsettled, as well as the linkage between hypothalamic leptin action and *Kiss1* expression (for review, see Hill et al. 2008).

Intriguingly, in mammals a further gene has recently been identified that potentially is involved in hypothalamic

regulation of seasonal gonadotropin secretion. The mammalian RFamide-related peptide gene (*RFRP*) is an ortholog of the avian gene encoding the gonadotropin-inhibiting hormone (GnIH), which suppresses gonadotropin release at the pituitary level in birds (Tsutsui et al. 2000). In different rodent species, including Syrian hamsters, GnIH administration has been demonstrated to suppress LH secretion (Kriegsfeld et al. 2006). In both Syrian as well as Djungarian hamsters, expression of *RFRP* in the MBH is photoperiodically regulated with low gene expression and reduced immunostaining of RFRP (RFRP-1, RFRP-3; gene products in mammals) in short photoperiod (Revel et al. 2008). This is astonishing insofar as the putative gonadotropin-inhibiting function would suggest peptide expression to be up-regulated. Although the hypothalamic site of *RFRP* expression suggests that melatonin might act directly on *RFRP*-expressing cells in Syrian hamsters (Hastings et al. 1988; Maywood and Hastings 1995), the reasonable assumption still has to be confirmed (Revel et al. 2008).

The loss of sensitivity to the inhibitory long melatonin signal in short photoperiod, i.e. photorefractoriness, occurs (spontaneously) already in winter (or after long-term exposure to SD) and hallmarks the switch to summer acclimatization. Accordingly, the photorefractory state provides the precondition for gonadal recrudescence, thus enabling an early beginning of the breeding season in spring. Different melatonin target sites have been demonstrated to develop refractoriness to melatonin in Djungarian hamsters (Freeman and Zucker 2001). The results indicated that the nucleus reuniens (NRE) and paraventricular nucleus (PVT) of the thalamus and the hypothalamic SCN became independently refractory. Lacking synchronization suggests that the temporal regulation might differ between the hormone systems involved in the hamsters' reversion to the summer phenotype. Ablation studies revealed that the SCN is likely to be involved in conveying the SD melatonin signal to the reproductive axis in Djungarian hamsters (Bartness et al. 1991). In contrast, in Syrian hamsters the dorsomedial hypothalamus appears to be the central site for the melatonin effect on seasonal reproduction (Maywood and Hastings 1995). Examinations of gene activity associated with photorefractoriness indicated that hypothalamic expression of thyroxine-binding proteins and thyroxine uptake might be critical for the regulation of reproduction (Prendergast et al. 2002).

Thyroid hormones: a central switch?

In the 1970s, many studies provided evidence that the thyroid hormones thyroxine (T_4) and triiodothyronine (T_3) play an important role in seasonal adaptations (Demeneix and Henderson 1978; LeBlanc and Villemaire 1970; Lynch et al. 1978; Maurel and Boissin 1979; Young et al. 1979). Thereafter only few investigations dealt with both seasonality and the hypothalamic–pituitary–thyroid axis (HPT). This is astonishing insofar as the symptoms of thyroid dysfunction, which have been known for a long time, are closely linked to the energy metabolism.

Basal metabolic rate (BMR) and thermogenic capacity are closely correlated with plasma concentrations of thyroid hormones. Correspondingly, winter-acclimatized Djungarian hamsters have significantly elevated plasma T_3 concentrations (Seidel et al. 1987), and hypothyroid hamsters display a diminished thermogenic capacity (Seidel and Heldmaier 1982). Furthermore, blocking of the formation of T_3 inhibits the cold-induced increase in UCP1 expression in brown fat (Reiter et al. 1990).

More than 70 years ago, the critical role of the thyroid for the annual cycle in reproduction has been demonstrated by removing the gland in ducks (Benoit 1936). The experiment was repeated later on with quails and starlings (Follett and Nicholls 1985; Goldsmith and Nicholls 1984) followed by sheep (Karsch et al. 1995; Webster et al. 1991a, b). Thyroidectomy prevented the typical responses of the gonadal system and body weight after a change in photoperiod. Injections of T_4 recovered the animals' responsiveness to photoperiodic changes. Moreover, it has been shown in sheep that thyroid hormones are involved in neuroendocrine processes responsible for seasonal suppression of pulsatile GnRH release (Anderson et al. 2002; Dahl et al. 1995; Webster et al. 1991b). Therefore, in this context, thyroid hormones were assumed to act directly on the brain. In fact, small doses of T_4 inhibited the secretion of LH only if applied centrally but not after peripheral injections in thyroidectomized sheep (Viguié et al. 1999). With the help of microimplants containing T_4, the target sites were localized in the premammillary and ventromedial preoptic area (Anderson et al. 2003).

For the hormones of the HPT axis, additional functions within the hypothalamus have been described since then, which cannot be considered here (Bechtold and Loudon 2007; for review, see Herwig et al. 2008). Initially, the photoperiodic control of hypothalamic gene expression critical for central thyroid hormone conversion has been shown in Japanese quails (*Coturnix japonica*; Yoshimura et al. 2003). Subsequently, several studies focusing on thyroid hormone metabolism provided evidence that the expression of two enzymes is critical for seasonal changes in mammals. The type 2 deiodinase (DIO2) converts T_4 to the more active T_3, whereas the type 3 deiodinase (DIO3) converts T_4 to inactive reverse triiodothyronine (rT_3) as well as T_3 to inactive diiodothyronine (T_2) (Lechan and Fekete 2005). Thus, the ratio of these two deiodinases regulates the availability of T_3 within the hypothalamus

(Bianco et al. 2002). A site of regulation was found in the basolateral wall of the third ventricle in rats, where the expression of *Dio2* mRNA was detected in specific glial cells (tanycytes) (Tu et al. 1997). With the finding that in young Djungarian hamsters (weanlings) *Dio2* was expressed in a photoperiod-dependent manner (Watanabe et al. 2004), the relevance for seasonal adaptations became apparent. However, the SD-induced decrease in *Dio2* presumably was due to the still immature state of the young males; in adult hamsters, *Dio2* expression was unaffected by photoperiod unlike the expression of *Dio3* (Barrett et al. 2007; Watanabe et al. 2007). Central T_3 availability seems to be achieved differentially in Djungarian and Syrian hamsters. In the latter species, short photoperiod negatively regulates *Dio2* expression (Revel et al. 2006) without any effect on the expression of *Dio3* (Barrett et al. 2007). In contrast to the LD-breeding hamsters, SD-breeding Saanen goats show reduced *Dio2* expression in long photoperiods, indicating low amounts of hypothalamic T_3 (Yasuo et al. 2006). Thus it appears that in both LD and SD breeders, the period of reproductive quiescence coincides with low concentrations of T_3 in the hypothalamus. The reasonable assumption that the central T_3 availability is a key determinant of seasonal transitions was convincingly confirmed via central application of T_3 (microimplants). Chronic replacement of T_3 in the hypothalamus of SD-exposed Djungarian hamsters prevented testicular regression and a decrease in body weight (Barrett et al. 2007). Only the change in fur colouration, which is controlled by the pituitary and prolactin secretion, was not affected.

Additional genes such as the ones encoding melatonin-related receptor GPR50, nestin and cellular retinol-binding protein (CRBP I) are seasonally expressed in the tanycytes of the ependymal layer (Barrett et al. 2006). The view of tanycytes being a crucial interface is also supported by the cells' property to take up molecules from the CSF (Rodriguez et al. 2005) as well as the fact that processes of tanycytes extend to the ARC and the median eminence bridging the gap between CSF and portal blood. Plasticity of the processes within the MBH is governed by photoperiod (Kameda et al. 2003). Morphological changes in tanycyte end-feet surrounding GnRH axon terminals indicate regulatory effects on the release of GnRH and, thereby, on secretion of gonadotropins.

The interesting question how the photoperiodic information reaches the tanycytes, remains. Indeed, melatonin concentrations in the liquor of the third ventricle do not only mirror the annual changes in signal duration but even are manifold higher than in blood (Skinner and Malpaux 1999). Melatonin receptors, however, are completely lacking in the ependymal layer including tanycytes (Morgan et al. 1994). Recent findings in LD-breeding Syrian (Yasuo et al. 2010) and European hamsters (Hanon

et al. 2010) as well as in SD-breeding soay sheep (Hanon et al. 2008) indicate that the thyroid-stimulating hormone (TSH) fills the gap between encoding of the photoperiodic information and the regulation of *Dio2/Dio3* expression in the ependymal layer. Intriguingly, the data strongly suggest that hypothalamic tanycytes receive information from melatonin-receptor-expressing cells in the pars tuberalis that release TSH in a photoperiod-dependent manner. The latter is in agreement with much earlier findings, which showed that TSH-like immunoreactivity in the pars tuberalis of Djungarian hamsters is increased in LD compared with SD (Wittkowski et al. 1988). It is worth mentioning that the proposed information flow does not correspond to the common model of hypothalamic control of the anterior pituitary, which is why the mechanism was assumed to have evolved before the evolutionary separation between the hypothalamus and the pituitary (Hanon et al. 2008). Moreover, the photoperiod-dependent mechanism of *Dio2* induction initially has been found in Japanese quail (Nakao et al. 2008), supporting the view of TSH release from the pars tuberalis to be an evolutionary conserved key element of photoperiodic regulation of reproduction.

Alternatively, one might speculate about a receptor-independent mechanism by which melatonin directly acts on tanycytes. Other scenarios might involve the orphan receptor GPR50, which is the mammalian ortholog of a melatonin receptor (Mel_{1c}) that has been found in fish, chicken and *Xenopus laevis* (for review, see Dufourny et al. 2008). Although GPR50 does not bind melatonin, a mediating function would be conceivable.

Concluding remarks

Since Axelrod (1974) described the pineal gland as a neurochemical transducer converting the neuronal signals coming from the eye into a humoral signal, our knowledge about the photoneuroendocrine system including the circadian system considerably expanded and now comprises many molecular details (for review, see Korf and Stehle 2005). The physiological role of melatonin to mediate the annual changes in day lengths via duration of nightly secretion is now generally accepted (Paul et al. 2008). Taking into account that several organ systems change their activity during seasonal transitions, it is evident that more than a single hormone system is responsible for activating and inactivating the multitude of physiological functions. In the process, melatonin solely encodes and mediates the environmental cue, and as a consequence, the organism then drives different hormone systems that arrange for the appropriate seasonal responses. There is convincing evidence that the thyroid hormones are key players within the seasonal coordination of diverse

functions such as the regulation of reproduction and energy balance, including the control of body weight, T_b, and basal metabolism. Due to recent findings, a more important role must be attributed to the pituitary gland, which appears to be crucial not only for seasonal variations in circulating prolactin and thereby changes in fur colouration, but also for the regulation of hypothalamic thyroid hormone availability, which in turn affects gonadal function. However, it remains to be elucidated how the thyroid hormones interact with the known hypothalamic pathways involved in the regulation of gonadal function, including kp/GPR54 signalling. This complex interaction of different hormone systems, which still raises many questions, makes mammalian seasonal adaptation such a fascinating research area keeping curiosity alive.

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